CH—ACIDS

A guide to all existing problems of CH-acidity with new experimental methods and data, including indirect electrochemical, kinetic and thermodynamic studies

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Preface

Almost all organic compounds are CH-acids because they contain C-H bonds the hydrogens of which are capable of being substituted by metals resulting in carbon-metal bonds. In other words, organometallic compounds are salts of CH-acids and the properties of CH-acids belong in the domain of organometallic chemistry. The authors have been working in this field for many years and this book is indeed addressed to organometallic and organic chemists. This does not necessarily mean that the authors wish to single out a particular audience; in fact, their aim is to explain their special interest in, for instance, proton transfer stereochemistry or structure vs. CH--acidity patterns. On the other hand, although there is a very direct relation between organometallic reactivity and CH-acidity, this problem is not treated in this book since this aspect of the problem of reactivity will already be well known to organometallic chemists.

The present book deals with the acidity proper, not with carbanion chemistry nor organometallic chemistry. Not all aspects of carbanion chemistry or organometallic chemistry pertain to CH-acidity, but both of the problems have much in common.

CH-acidity characterises thermodynamic stability of carbanions in a medium containing a proton donor as carbanion acceptor. Many other acceptors may be employed for the purpose, e.g. Hg^+, Ag^+, RHg^+, and other, cations. However, proton donors are the most convenient to deal with since, firstly carbanion affinity for the proton was the easiest to determine experimentally and, secondly, the data obtained are comparable with a wealth of data available on OH- and NH-acidities and, thus, the stability of carbanions may be collated with the stability of O-, H-, and other anions in various solvents and in the gas phase.

A problem currently being worked on is the experimental determination of acidity in the gas phase, which would make it possible to construe a quantitative intrinsic acidity scale not influenced by solvent. The first results of this work have already been obtained using the ion cyclotron resonance method (to be discussed in Chapters I and II). The acidity series in the gas phase has been found to be quite different from that obtained in solution.

Acidity in solution is of special importance because organic chemistry is, in the main, the chemistry of solutions. Dimethyl sulphoxide, liquid ammonia, cyclohexylamine, and some other solvents are excellent for a study of CH-acidity and it is in these solvents that most data on equilibrium and kinetical acidities has been obtained. However, pKa values found in cyclohexylamine correspond to ion-paired rather than dissociative acidity; O-bases in dimethylsulphoxide are ion-pairs of alkali cations and this also affects pKa's of CH-acids measured in a dimethylsulphoxide/O-based system.

On the whole, the effects of ion-pair formation upon equilibrium CH--acidity have not been exhaustively studied and, in this direction, there is still much to be done, especially on the theoretical level.

The first two chapters of the book discuss equilibrium CH-acidity. Chapter I describes methods to study equilibrium acidity and the pKa values of numerous CH-acids are tabulated. The determination of the acidity of weak acids such as CH-acids lead to difficult experimental problems which are concerned with a large pKa scale depending on CH-acid structures. An important task, therefore, is a search for new direct or indirect approaches to determining relative acidities. Recently, a great amount of published work has appeared in this field and this is discussed in Chapter I. It should be noted that for the most part the methods available may be applied only in a rather narrow pKa interval whereas the problem of creating a general-purpose method capable of giving the pKa of any acids with a wider pKa interval still awaits solution. Chapter II discusses equilibrium acidity as a function of CH-acid structures.

In Chapter III, the hydrogen isotope exchange in CH-acids, i.e. the so-called kinetic CH-acidity is discussed. Isotope exchange is discussed as a method of finding the relative reactivity of C-H bonds in a series of CH-acids studied in one and the same solvent base system.

Chapter IV is devoted to the sterochemistry of proton transfer in CH-acids. Proton transfer from tetrahedral carbon atom allows one to understand better the nature of transition states and the role played by ion-pairing and solvation. Stereochemical problems are specific to CH-acids; they do not arise when studying acids of other types and in this aspect there is a significant difference between CH-acids and OH- or NH-acids. The stereochemical aspect is an essentially new aspect contributed by CH-acids in a study of acidity on the whole.

Equilibrium vs. kinetic acidity is discussed in Chapter V. The authors believe that the Brönsted equation is a fundamental law but there are numerous factors obscuring experimental observation of the action of this law. These factors are discussed extensively. Anomalous Brönsted slopes observed in some cases are explained by effects of the medium indicating again the importance of studies of rates and equilibria in the gas phase.

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Chapter I

Equilibrium Acidity of CH-Acids

I. INTRODUCTION

Almost any organic compound can, when acted upon by a base (a proton acceptor) of appropriate strength, ionise in solution to give carbanions, that is, negatively charged species whose charge is totally or (more often) partially localised on one of the carbon atoms. This property of CH-bonds gives rise to a great variety of organic reactions in which proton abstraction is a limiting or a pre-equilibrium step. Some examples are carbonyl-methylene condensations, trans-metalation reactions, the allyl rearrangement, cyclisation/recyclisation rearrangements, etc.

Shatenshtein[1] was the first to consider hydrocarbons in terms of the general theory of acids and bases. The recent decade has brought a number of surveys of CH-acidity[2,5], among which the monograph by Cram[2] may be mentioned.

It is proposed to use the term "acidity" instead of the alternative "acid ionisation constant", in order to emphasise the relation between the equilibrium (thermodynamical) acidity (acid ionisation constant, K_a)

$$RH + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^- + HB \qquad pKa = -\log \frac{k_1}{k_{-1}}$$

and the kinetic acidity (k_1), the rate of proton abstraction from the acid molecule. The equilibrium and kinetic acidities, i.e. the quantities pK_a and $\log k_1$, often vary in parallel.

To begin with, consider equilibrium CH-acidity. It does not depend on a proton abstraction mechanism and is the best characteristic of the thermodynamical stability of carbanions in a given system. In solution, the energy of any species participating in the acid-base equilibrium should be corrected for the solvation energy. It is advantageous therefore to consider first acid-base equilibria in the gas phase as this reflects the "intrinsic" CH-acidity and is not affected by solvation. Following this, this Chapter will deal with acid-base equilibria in solution.

The acidity of any acid in the gas phase may be written as[6]

$$X^-(gas) + H^+(gas) \rightleftharpoons HX(gas) + \Pi$$

where Π is affinity for proton.

The Π value is the enthalpy of proton addition to the anion and may be

represented in the following form,

$$\Pi = -\Delta H_{HX} + \Delta H_{X^-} + \Delta H_{H^+}$$

where ΔH_{HX}, ΔH_{X^-}, and ΔH_{H^+} are the enthalpies of formation of HX, X^- and H^+ respectively. The heat of proton formation, $-\Delta H_{H^+}$, is the heat of the following reaction.

$$(1/2)H_2 \rightleftharpoons H^+(gas) + e^-(367 \text{ kcal gram-ion}^{-1} \text{ in vacuo}).$$

ΔH_{HX} can be found from experiments directly, while the heat of formation of anions in the gas phase may be obtained by, e.g., the Yatsimirskii[7] method that assumes that the energy of a salt crystal lattice is the enthalpy of transformation of the solid salt to the ion gas consisting of the same ions

$$U_{KA} = -\Delta H^o_{KA} + \Delta H^o_{K^+} + \Delta H^o_{A^-}$$

where $-\Delta H^o_{KA}$, $-\Delta H^o_{K^+}$, and $-\Delta H^o_{A^-}$ are the heats of formation of the crystalline salt, gaseous cation and gaseous anion, respectively. The crystal lattice energy is given by the Fayance equation.

$$U_{KA} = H_{K^+} + H_{A^-} - L \text{ solv.}$$

where H_K and H_A are the heats of ion hydration and L_{solv} is the heat of solution of the salt at the ion strength of zero.

The data on the heats of formation and on crystal lattice energies allow one to calculate the energy of formation of ions in vacuo and the proton affinities of the anion, the latter not usually being obtainable by direct experiment.

The proton affinity may be found through the following thermodynamical sequence[3,8].

HX	$\longrightarrow X^{\cdot} + H^{\cdot}$	(DH)
$X^{\cdot} + e^-$	$\longrightarrow X^-$	(-EA)
$H^{\cdot} + e^-$	$\longrightarrow H^+$	(IP)
Sum: HX	$A^- + H^+$;	$-\Pi$=DH-EA+IP

where DH is the X-H bond energy, EA is the affinity for electron of the radical X and IP the ionisation potential of hydrogen. Recently, Brauman[8] and other workers[9] using the ion cyclotron resonance technique have determined the affinity for the electron for a number of radicals and employed the thermodynamical sequence described above for calculating the values for a number of element hydrides. These data, together with the calculations performed using the method of Yatsimirskii[7] are listed in Table 1.

TABLE 1

Proton Affinities for some Anions at Medium Vacuum [6-9]

Anion	Π kcal/mole		Anion	Π kcal/mole	
	refs 6, 7	refs 8, 9		refs 6, 7	refs 8, 9
CH_3^-	-	-	HS^-	343	350
NH_2^-	419	407	CH^-	325	333
OH^-	383	390	NO_3^-	320	-
F^-	363	370	Br^-	315	324
PH_2^-	-	364	I^-	307	314
$RCOO^-$	about 350	-	HSO_4^-	296	-
CN^-	348	-	ClO_4^-	285	-

The data in Table 1 suggests that the acidity of hydrides in vacuo should rise in going from the left to the right in the Periodic System and downwards in each of the Groups.

The data obtained may be summarised to give the series in which Brönsted acids are arranged in the order of the decrease in acidity at medium vacuum at 300°K, [9b].

$n\text{-}C_4H_9SH > CH_3NO_2 >$ cyclo-$C_5H_6 > CHCl_3 > CH_3OOCH_3 > CH_3CN > CH_2Cl_2$, $CH_3SOCH_3 \geq C_2H_6$, tert-C_4H_9OH, iso-$C_4H_9OH > C_2H_5OH > CH_3OH > C_3H_4$, $C_6H_5CH(CH_3)_2 > C_6H_5CH_3 > C_3H_6 > H_2O > C_6H_6 > H_2 > NH_3 > C_2H_4$, C_6H_{12} $> (CH_2)_3$, CH_4

This series is in dramatic contrast with the usual acidity concept based on studying aqueous and alcohol solutions of acids. Thus the alcohol acidity series in the gas phase [10,11].

$$t\text{-BuOH} > i\text{-PrOH} > EtOH > MeOH > H_2O$$

is the reverse of the series obtained in hydroxyl-containing solvents,

$$H_2O > MeOH > EtOH > i\text{-PrOH} > t\text{-BuOH}$$

Consequently, the methyl group effect in the gas phase disagrees with the conventional (+I)-pattern. Brauman and Blair[10] introduced an electrostatic model to explain the methyl-induced stabilisation of alkoxide ions. The model includes the interaction of charge with polarisable alkyl groups and predicts that an increase in the size of R in the group RO^- should lead to an increase in the R polarisability and to a decrease in the anion potential

energy ("inner solvation").

The R polarisability effect is not observed in hydroxyl-containing solvents because the energy of solvation ("outer solvation") of the negative oxygen with hydrogen bonds is markedly higher than is the energy of interaction of the ion spearhead with the dipole induced by it.

The weakest acid in the series discussed above is methane. The acidity rises, however, when one of the hydrogens is replaced by a group that may stabilise the carbanion. Thus the introduction into methane of an electron withdrawing chlorine atom may place the CH-bond value beneath the ammonia - Π value, $CH_3Cl > NH_3 > CH_4$, while toluene, whose phenyl group stabilises the negative charge via a conjugation mechanism, is a stronger acid than is water [13]. Accordingly, cumene in the gas phase is stronger than methane, i.e., alkyl groups do not obey the (+1)-pattern assumed for them conventionally.

The energies in Table 1 and the qualitative series given above, when collated, lead to the following acidity series in the gas phase.

$HBr > RSH, H_2S > HCN > CHCl_3 > CH_3CN \geq HF, CH_2Cl_2, CH_3SOCH_3 >$ alcohols $> C_6H_5CH_3 > H_2O > C_6H_6 > NH_3 > CH_4$

The position of hydrogen fluoride in the series is due to the fact that fluorine ion in $Et_4NF.2H_2O$ can split a proton from, e.g., acetonitrile[13].

$$CH_3CN + Et_4N^+F^- \rightleftharpoons ET_4N^{+-}CH_2CN + HF$$

The position of hydrogen fluoride agrees with the results published recently by McIver and Miller[158] whose data allow one to arrange alcohols, acetylenes, and hydrofluoric acid in the following series in the gas phase at 298°K.

$(CH_3)_3CCH_2OH > HF >$ t-BuOH > i-PrOH > t-BuC $\equiv$ CH > PrC $\equiv$ CH > EtOH $> CH_3C \equiv CH >$ MeOH

The series demonstrates that no distinction exists between CH-acids and acids of other types in the gas phase and all the types are arranged randomly. The same conclusion was reached by Ritchie and King[14] who calculated the potential energy surfaces for simpler reactions involving the hydride ion attack along the X-H bond axis.

$$X — H \leftarrow - - H^- \quad (X=H,F,OH,NH_2,CH_3).$$

Water, ammonia, and methane were found to behave similarly, except that the energy differences between the reactants and the proton transfer products were different.

Consequently, hydrocarbons and their derivatives are not less efficient at displaying their acid properties than are hydrides and substituted hydrides of other elements. In this respect acetic acid may be regarded as an acetylated oxygen hydride (water).

In hydroxyl-containing solvents, however, the acid properties of hydrides and substituted hydrides of electronegative elements(e.g., OH-acids) are

much more pronounced than are CH-acidities. Hydroxyl-containing solvents favour the ionisation of OH-acids because they can form hydrogen bonds with electronegative elements. The next Section will compare CH- and OH-acidities in water.

II. CH-ACIDITIES IN WATER. A COMPARISON WITH HYDROXY ACIDS

Toluene in the gas phase is a markedly stronger acid than is water[12]. It is profitable to consider whether in a hydroxyl-containing solvent toluene is a stronger or weaker acid than water[15]. The acid-based equilibria in these systems may be written in the following form.

$$H_2O.solv + B.solv \rightleftharpoons HB^+.solv + OH^-.solv$$

$$PhCH_3.solv + B.solv \rightleftharpoons HB^+.solv + PhCH_2^-.solv$$

To calculate dissociation or ionisation constants in solution, it is necessary to include the solvation of all the equilibrated species, both on the right and on the left hand side of the equations. When the proton acceptor, B, is one and the same and both reactions are made in the same solvent, then the calculation of relative acidities of water and toluene will deal only with the toluene and water solvation energies (on the left) and the hydroxyl and benzyl anion solvation energies (on the right).

The difference between solvation of water and toluene in hydroxyl-containing solvents is a result of the fact that the solvation is mainly due to hydrogen bonding. Eigen has grouped the following series as a measure of the ability to form hydrogen bonds[16], OH... O > OH... N, NH ....O > NH....N > SH....X, XH ....S > PH....X, XH ...P > CH.....X, XH....C where X is any element.

It is clear from this tabulation that OH- and CH-acids lie at the opposite ends of the series; the former acids are the strongest, the latter ones the weakest hydrogen bond donors. Consequently, the water energy decreases more than does the toluene energy, on going from the gas phase to a hydroxyl-containing solvent such as water.

Similarly, O-bases are the strongest while C-bases are the weakest hydrogen bond acceptors, so the hydroxyl ion energy decreases more than does the benzyl anion energy on going from the gas phase to aqueous solutions.

Probably, the main effect on relative acidities of water and toluene in water is the anion solvation difference. Parker[17] who studied reactions and equilibria in which anions participated showed that the solvent-induced increment in the anion solvations provides the most important contribution in the energy. The hydroxide ion, a small ion with a localised charge, is solvated with water very effectively whereas the benzyl anion whose charge is delocalised would have solvated less had it not been protonated instantaneously. This agrees with the hard and soft acids and bases principle introduced by Pearson[18]. As a result, the difference between the solvation energies of hydroxyl ion and water exceeds noticeably the difference between the solvation energies of toluene and the benzyl anion. In other words, a hydroxyl-containing solvent favours the $H_2O \rightarrow OH^-$ transformation much more than it does so with $PhCH_3 \rightarrow PhCH_2^-$. Therefore, the equilibrium in the water phase as compared with the gas phase is shifted to the right for water much more significantly than it is for toluene.(Table 2).

TABLE 2

Water and Toluene Acidities as a Function of Solvation in changing from the Gas to the Liquid Water Phase [15]

Extent of solvation of an ion or a molecule		Total acidity increment
H_2O	OH^-	high
high	very high	
$PhCH_3$	$(PhCH_2^-$	small*
poor	(poor)	

* That is why the anion is "instantaneously" protonated in water.

As a consequence of this, solvation effects in the aqueous phase appreciably increases the acidity of water, a weak acid in the gas phase, whereas toluene does not reveal its acid properties, that is, it remains as weak an acid as it was in the gas phase.

It can be concluded that the benzyl anion is a "strong base" although "strong base in water" would be more to the point since it has already been seen that both bases are strong in the gas phase.

This example shows why CH-acids in water are markedly weaker than are OH-acids. This is illustrated in Table 3 which compares CH- and OH-acidities for similar structures. In water, the acidities of the CH-acids are, on the average, 20 pKa units lower than those of the respective OH-acids.

TABLE 3

Substituent effect on acidities of related OH- and CH-acids; pKa=-logKa; ΔpKa's correspond to the differences between pKa's of CH- and OH-acids of similar structure; All pKa's (except for methane) are based on the equilibria

$$H\text{-}OR + H_2O \rightleftharpoons OR^- + H_3O^+$$

and

$$H\text{-}CH_2R + H_2O \rightleftharpoons CH_2R^- + H_3O^+$$

Acid	pKa	ΔpKa	Reference
H-OH	15.7	>25	
$H\text{-}CH_2H$	>40*		2
$H\text{-}OCOCH_3$	4.7	ca.16	19
$H\text{-}CH_2COCH_3$	ca.21		2
H-OCN	3.7	ca.20	20
$H\text{-}CH_2CN$	ca.24		2
$H\text{-}ONO_2$	ca -7	ca.17	21
$H\text{-}CH_2NO_2$	10.2		22

* See section III of this Chapter.

However, there do exist CH-acids which are strong even in water. Table 4 lists pKa values for some CH-acids measured in water; much more extensive data on the subject have been published by Ebel[23].

TABLE 4

CH-Acidities in water at 25°C

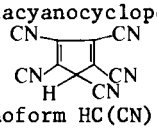
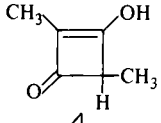
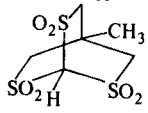
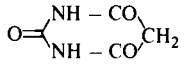
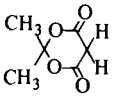
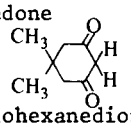
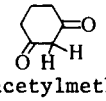
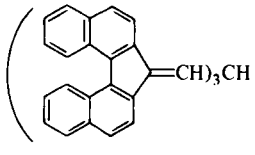
	Compound	pKa	Reference
1.	Pentacyanocyclopentadiene 	(-II)	24
2.	Cyanoform $HC(CN)_3$	(-5,13)	25
3.	Nitroform $(HC(NO_2)_3$	0.17	26
4.	Acid dimer of methyl ketene 	2.8	27
5.		3.30	28
		3.57	29.30
		3.60	31
6.	Dinitromethane $CH_2(NO_2)_2$	3.47	32
7.	Barbituric acid 	4.0	33
8.	Trifluoroacetylacetone $F_3C-CO-CH_2COCH_3$	4.7	34
9.	Meldrum acid 	4.83 (mixed acidity)	33
		2.49 (enol)	
10.	1,1-Dinitroethane $CH_3C(NO_2)_2H$	5.21	31
11.	Nitroacetone $O_2N-CH_2-CO-CH_3$	5.1	34
12.	Dimedone 	5.23 (pure enol)	
13.	Cyclohexanedione-1,3 	5.26	36
14.	Triacetylmethane $HC(COCH_3)_3$	5.81	37
15.	Tris(7H-(dibenzo/c,g/fluorene)-ylidenemethyl) methane 		37

TABLE 4 (continued)

Compound	pKa	Reference
16. Ethyl fluoronitroacetate $NO_2FHCCOOC_2H_5$	6.28	39
17. Phenylnitromethane $C_6H_5CH_2NO2$	6.8 3.89 (aciform)	40
18. Dibenzoylmethane $C_6H_5COCH_2COC_6H_5$	8.95	41
19. Tetramethylmethylene-disulphonium $(CH_3)_2\overset{+}{S}-CH_2-\overset{+}{S}(CH_3)_2$	9.00	42
20. Acetylacetone $CH_3COCH_2COCH_3$	8.94 8.13 (enol)	35, 37
21. HCN	9.3	21
22. Nitromethane CH_3NO_2	10.21 10.24 10.1	22 43 44
23. Acetoacetic ester $CH_3COCH_2COOC_2H_5$	10.49 8.09 (enol)	35
24. Dicyanomethane $CH_2(CN_2)$	11.19	34
25. Bis(phenylsulphonyl) methane $C_6H_5SO_2CH_2SO_2C_6H_5$	11.21	45, 46
26. Malonic ester $H_2C(COOC_2H_5)_2$	13.30	34
27. Water H_2O	15.7	
28. Cyclopentanone 	16.7 11.8 (enol)	47
29. 4,4',4"-Trinitrotriphenylmethane $(4\text{-}NO_2C_6H_4)_3CH$	17.44 (in alcohol)	48

The CH-Acids listed at the start of Table 4 are comparable in their strength with inorganic acids such as perchloric and sulphuric acids. It is noteworthy that Table 4 contains few unsubstituted hydrocarbons. Except for the Kuhn hydrocarbon (No. 15 Table 4) all of the compounds have acidifying groups with electron-acceptor heteroatoms. Other compounds of the Kuhn type are shown in Table 21.

The equilibrium acidities of alkanes, alkenes, arenes, cycloalkanes and other weak CH-acids cannot be measured in hydroxyl-containing solvents. Molecules of H_2O in water have a rather high acidity (pKa 15.7). The acidities of hydrocarbons are usually measured in aprotic solvents. Methods for carrying out this measurement will be discussed in Section III.

III. METHODS OF MEASURING IONISATION EQUILIBRIA OF CH-ACIDS

Equilibrium acidity is a function of the equilibrium between an acid and the conjugated base. Equilibrium acidities of hydrocarbons are usually obtained from trans-metalation reactions in solvents of low polarity and low proton-donor activity, such as ether, benzene, liquid ammonia, cyclohexylamine, dimethylsulphoxide, etc.

$$R\text{-}H + R'\text{-}M \rightleftharpoons R\text{-}M + R'\text{-}H$$

(M is Li, Na, K, Ca,; R is Alk, Ar, aralkyl, etc; R' is Alk, Ar, cyclo-$C_6H_{11}NH$, NH_2 etc.)

In 1908 Shorygin showed that ethylsodium will metalate benzene, toluene, and diphenylmethane[49]. This showed that methane is a weaker acid than are the other three. Following this, numerous qualitative data of the same kind were obtained; e.g., potassium amide in liquid ammonia did not metalate toluene but did metalate diphenylmethane[50], amylsodium reacted with benzene while phenylsodium, in turn, did so with toluene[51]. These data have been summarised in the acidity series[52] pentane (or ethane) < benzene < toluene < NH_3 < diphenylmethane.

Much of this information was obtained in the late thirties[53-58]. However, it is only recently that a quantitative approach has been made by Conant and Wheland [59], and McEven[60] in their classical papers on this subject.

1. Trans-Metalation Equilibria

To estimate the relative acidities of hydrocarbons, Conant and Wheland[59] employed colorimetry. Conant and Wheland studied the equilibria of sodium or potassium salts of CH-acids in ether and McEven used benzene.

$$R - M + R'\text{-}H \underset{\text{ether or benzene}}{\overset{25^\circ}{\rightleftharpoons}} R\text{-}H + R'\text{-}M \qquad (1)$$

The salts RM and R'M absorb at different wavelengths, so the concentrations of these may be measured colorimetrically. The change in colour is, as a rule rapid, but in some cases (especially with sodium salts) many days are necessary for the equilibrium to be achieved. With the equilibrium (1) we have

$$pKa(RH)-pKa(R'H) = -\log \frac{[RM]}{[RH]} + \log \frac{[R'M]}{[R'H]} \qquad (2)$$

At first McEven[60] believed that RM and R'M dissociated to the same extent whereas CH-acids did not dissociate at all. This led him to develop the following equation.

$$pKa(RH) - pKa(R'H) = -\log \frac{[R^-]}{[RH]} + \log \frac{[R'^-]}{[R'H]}$$

Later it was shown, however, that the sodium or caesium salts of fluorene in tetrahydrofuran at 25°C are intimate ion-pairs while the lithium salt is a solvent-separated ion-pair. Its visible spectrum coincides with, while the ultraviolet spectrum differs from, the spectra of the intimate pairs[62]. The electroconductivity data show that the fluorene salts dissociate to a small extent only. Thus, the change in colour observed by McEven[60] was due to ion-pairs rather than free ions, in other words, the Cram[2] equation (eq. 2) is valid.

Equation (2) says that the acids RH and R'H differ by two pKa units when the visual observation shows approximately 91% extent of metalation at the initial concentrations ratio of 1:1. If the same extent of metalation is achieved at a five-fold excess of R'H, the difference will be just 0.4 pKa units.

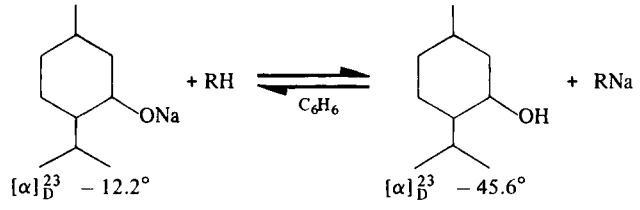
McEven[60] compared many pairs of CH-acids. He also collated the colorimetry data with the carboxylation data. The position of the equilibrium between

the acids and their salts was estimated by carboxylation of the equilibrium mixture and by measuring relative yields of the acids.

$$\begin{array}{ccc} RH + R'M & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & RM + R'H \\ CO_2 \downarrow k_2 & & CO_2 \downarrow k_3 \\ R'COOM & & RCOOM \end{array} \qquad (3)$$

It is evident that the method is applicable only when k_2 and k_3 are much greater than k_1 and k_{-1} (eq. 3). Both methods gave coherent pKa values for various pairs of CH-acids.

McEven[60] also employed polarimetry, to find and establish the equilibrium between sodium menthylate and various CH- or OH-acids, or between menthol and the sodium salts of CH- or OH-acids in benzene.



(sodium l-methylate) (l-menthol)

He succeeded in deriving a relationship between OH-, CH- and NH- acidities and working out a general acidity scale embracing methanol through cumene.

McEven's[60] basis for the calculation of acidities of the weaker acids was a pKa value for methanol of 16[63]. He noted that his pKa's were the minimal values, owing to assumptions inherent in the colorimetry method employed. McEven's scale is shown in Table 5. For a long time, it was the only one in use.

Streitwieser and his co-workers[64,65] developed a different scale of equilibrium acidity, also based on trans-metalation reaction. Streitwieser measured equilibrium constants for lithium (caesium) cyclohexylamide and CH-acids and for lithium (caesium) salts of CH-acids and cyclohexylamine. The solvent used was cyclohexylamine.

$$RH + \text{cyclo-}C_6H_{11}\overset{-}{N}H\overset{+}{M} \rightleftharpoons RM + \text{cyclo-}C_6H_{11}NH_2$$

Both the scales, obtained in media of low polarity, reflect ion-pair CH--acidity, in other words, acid ionisation rather than acid dissociation was operative. The ion-pair acidity is a better reflection of the "intrinsic" acidity if solvent-separated rather than intimate ion-pairs are formed because, if intimate ion-pairs are formed, a partial covalent bonding will contribute in the bonding between the metal and the organic group in the organic compound participating in trans-metalation. Streitwieser et al[64,65] believe that covalent bonding between polyarylmethane anions and alkali metal cations may be neglected in cyclohexylamine, and argue as follows.

TABLE 5

McEven's Scale of Acidity[60]

Compound	pKa	Compound	pKa
Methanol	(16)	Diphenylamine	23
Pyrrol	16.5	Fluorene	25
Benzyl alcohol	18	Aniline	27
Ethyl alcohol	18	p-Toluidine	27
Benzhydrol	18	p-Anisidine	23
Isopropanol	18	Xanthene	29
Triphenylcarbinol	19	9-Phenylxanthene	29
Tert-butanol	19	Diphenylbiphenyl-methane	31
Tert-amyl alcohol	19	Triphenylmethane	33
Menthol	19	Diphenyl-(α-napthyl) methane	34
Acetophenone	19	Diphenylmethane	35
9-Phenylfluorene	21	1,1-Diphenylethane	36
9-(α-Napthyl)fluorene	21	Cumene	37
Phenylacetylene	21		
Indene	21		

The salts absorb at much higher wavelengths than do the respective hydrocarbons, in other words, conjugation increases when salt formation occurs. Further, solutions of the salts usually obey the Lambert-Beer law in a wide concentration range*. Thirdly, a decrease in the solvent polarity leads to a hypsochromous shift of 30-70 nm due probably to changes in solvation of the ion-pair cation[65]. But the most crucial evidence is that although lithium and caesium cations differ markedly in their electronegativities and ion radii, the spectra are practically independent of the cation taken. The electroconductivity of fluorenyllithium is very close to that of lithium perchlorate, in cyclohexylamine[66].

The spectral data obtained by Streitwieser et al have been summarised by Unmack[63]. This led to an assumption that the formation of covalent bonds in the lithium or caesium ion-pairs may be neglected in cyclohexylamine and that the equilibrium constants found from the spectra are a measure of acidity[63]. The constants were converted to the pKa values by using 9-phenylfluorene (pKa 18.5) as an arbitrary reference.†

* The law is violated with p-biphenylyldiphenylmethane, triphenylmethane, diphenylmethane, and lithium cyclohexylamide in cyclohexylamine.

† pKa 18.5 (aqueous sulpholane[67]), 18.59 (the H_-function in DMSO-EtOH or DMSO-H_2O[68,69]) 19.1 (H_- in DMSO-MeOH[70]), 16.4 (potentiometrically in DMSO[104]).

The respective data are listed in Table 6.

TABLE 6

Streitwieser's Scale of Acidity

Compound	pKa
9-Phenylfluorene	(18.5)
3,4-Benzofluorene	19.4
1,2-Benzofluorene	20.0
4,5 Methylenefluorene	22.6
Fluorene	22.8
2,3-Benzofluorene	23.2
1,1,3-Triphenylpropene	26.4
9,9-Dimethyl-10-phenyldihydroanthracene	28.0
p-Biphenylyldiphenylmethane	30.2
Triphenylmethane	31.5
Diphenylmethane	33.1

The Streitwieser scale is an order more accurate than the McEven scale; originally, it embraced a rather small number of hydrocarbons (polyaryl methanes and structurally related compounds).

Recently Streitwieser has included in his scale heterocyclic compounds and acetylenes[71-74]. The data (ion-pair acidities) are summarised in Table 7. Comparing the data of Tables 5 and 6 shows that the acidities of polyarylmethanes in ether, benzene, and cyclohexylamine are very close to each other, in other words, solvation factors only slightly affect pKa in these solvents. A drawback of both scales is that weak CH-acids such as monoarylmethanes, alkenes, arenes, and alkanes cannot be included in them.

TABLE 7

Streitwieser's CH-acidities[a]

CH-acid	pKa	Reference
N-Methylthiazolium iodide	14	72
Benzothiazole	28.08	74
Thiazole	29.50	74
Benzofuran	36.84	74
Benzothiophene	37.05	74
Thiophene	38.42	74
Toluene[b]	(40.9)	74
Benzene[b]	(43.0)	73
Pentafluorobenzene	25.85	78
$1,2,3,4\text{-}C_6F_4H_2$	31.52	73
$1,2\text{-}C_6F_2H_4$	34.98	73
PhC≡CH	23.20	71
t-BuC≡CH	25.48	71

[a] See also Tables 42 and 43 in Chapter III
[b] estimated indirectly via the Brönsted equation.

Filler and Chen Shen Wang[75] applied the Streitwieser system (cyclohexylamine/lithium cyclohexylamide) to polyfluorinated tri- and diphenylmethanes and to other compounds. The equilibrium acidities found are shown in Table 8.

TABLE 8

Streitwieser's Equilibrium Acidities for polyfluorinated Aromatic Compounds[75]

Compound	pKa
$(C_6F_5)_3CH$	15.8
$(C_6F_5)_2CH_2$	21.3
$(p\text{-}CH_3C_6F_4)_3CH$	17.9
$(p\text{-}CH_3OC_6F_4)_3CH$	19.3
$(C_6F_5)_2CHCH(C_6F_5)_2$	22.7

Shatenshtein and his team[76 77] studied ortho-, meta-, and para-carborane derivatives in ether, dimethoxyethane, and in cyclohexylamine. The pKa values they obtained are almost independent of the solvent. Table 9 lists acidities of carboranes in dimethoxyethane in terms of the Streitwieser scale.

TABLE 9

Streitwieser's Equilibrium Acidity for Carboranes in Dimethoxymethane against a Potassium Fluorenylide base[a],25°C

Compound	pKa
9,10-Dichloro-o-carborane	16.3[b]
1-Phenyl-o-carborane	22.6
1-Methyl-o-carborane	23.1
o-Carborane	23.3
1-Isopropyl-o-carborane	23.9
1-Phenyl-m-carborane	27.5[c]
1-Methyl-m-carborane	27.9[c]
m-Carborane	27.9[c]
p-Carborane	30.0[c,d]

[a] Lithium fluorenylide leads to pKa's by 1-2 units lower.
[b] With lithium fluorenylide.
[c] With potassium 9-phenylzanthylide.
[d] The pKa is 31.0 in cyclohexylamine.

The acidity of carboranes remains almost unaffected on going from dimethoxyethane to ether as solvent[78]. A wider range of ether solvents was studied with 9,10-dihydroanthracene, pKa 30.4 (Streitwieser scale), and diphenylmethane[79]. The pKa's of the hydrocarbons in diglyme, dimethoxyethane, ether, or in cyclohexylamine varied by 0.5 pKa units. 9,10-Dihydrosilaanthracene has a Streitwieser pKa of 27.4[80].

Shatenshtein et al[81] also found the acidity of potassium (3)-1,2--dicarbadodecahydronidoundecaborate[81]. The acid properties were, probably, due to the hydrogen bonded with five atoms (three borons and two carbons) of the pentagonal plane of the truncated ikosahedron,

$$B_9C_2H_{12}^-K^+ + A^-K^+ \rightleftharpoons B_9C_2H_{11}^{2-}K_2^+ + HA$$

where HA is fluorene or indene.

The Streitwieser pKa of this compound is 21.3, so this is a rather strong acid despite the presence of a high negative charge.

The data discussed above show that the McEven scale and, particularly the scale of Streitwieser have found a wide application. However, the trans--metalation method does not permit the study of weak CH-acids such as alkanes, arenes, alkenes, or CH-acids containing base-sensitive groups. The first attempt at carrying out indirect estimates of very low acidities was made by Cram[2]. His general purpose scale, discussed below, embraced the data of McEven and of Streitwieser (trans-metalation equilibria) as well as the results of Dessy and his co-workers, and Applequist and O'Brien[82].

2. The Cram MSAD Scale

Direct measurements of ionisation equilibria for alkanes, alkenes, and other weak CH-acids are experimentally very difficult. Applequist and O'Brien[82] laid the groundwork for a good method. These workers measured equilibrium constants between iodobenzene and various alkyl-, alkenyl-, aryl-, or aralkyllithium compounds in ether or in ether/pentane mixtures at -70°C, In this work Applequist and O'Brien[82] utilized the fact that there is a linear relationship, with a slope of unity between anion affinities for the proton and the I^+ cation[171].

$$R\text{-}Li + PhI \overset{K_{Ap}}{\rightleftharpoons} R\text{-}I + Ph\text{-}Li$$

The negative logarithms of the constants K_{Ap} are listed in Table 10.

TABLE 10

Logarithmic Equilibrium Constants for Iodobenzene & RLi (K_{Ap})[82] and diphenylmercury & R_2Mg (K_{De})[171]

R	$\lg K_{Ap}$	$\lg K_{De}$
cyclo-C_5H_9	6.90	-
cyclo-C_4H_9	6.14	-
neo-C_5H_{11}	5.46	-
iso-C_4H_9	4.59	-
iso-C_3H_7	-	6
n-C_3H_7	3.88	-
C_2H_5	3.50	4
CH_3	-	2
cyclo-C_3H_5	0.98	0.9
C_6H_5	0	0
$CH{=}CH_2$	-2.41	0.5
$CH_2CH{=}CH_2$	-	-0.2
$CH_2C_6H_5$	-	-0.4

Another method was introduced by Dessy and his group[83 84] who estimated equilibrium constants for dialkyl-, dialkenyl-, or diarylmagnesium compounds and diphenylmercury in tetrahydrofuran at 25°C. Relative logarithmic equilibrium constants (K_{De}) for this reaction are listed in Table 10.

$$R_2Mg + Ph_2Hg \overset{K_{De}}{\rightleftharpoons} 2\ RMgPh$$

The data obtained by Applequist[82] and by Dessy[83 84] were employed by Cram[2] to obtain the relative stabilities of anions of very weak CH-acids. Cram[2] felt that there was an inherent coherence between the data obtained by Applequist[82] and by Dessy[83 84], and the kinetic acidity of alkanes. His rationalisation of the evidence led to the first general-purpose acidity scale which included weak acids such as saturated hydrocarbons. The Cram scale, termed by him MSAD (McEven-Streitwieser-Applequist-Dessy), is shown in Table 11.

TABLE 11

The Cram MSAD Scale

CH-acid	pKa	CH-acid	pKa
Fluoradene	11	Ethylene	36.5
Cyclopentadiene	15	Benzene	37
9-Phenylfluorene	18.5	Cumene (α)	37
Indene	18.5	Triptycene (α)	38
Phenylacetylene	18.5	Cyclopropane	39
Fluorene	22.9	Methane	40
Acetylene	25	Ethane	42
1,3,3-Triphenylpropene	26.5	Cyclobutane	43
Triphenylmethane	32.5	neopentane	44
Propylene(α)	35.5	sec-Propane	44
Toluene (α)	35	Cyclopentane	44
Cycloheptatriene	36	Cyclohexane	45

It has been noted already that the data of Applequist and Dessy agree well, with an exception of the vinyl group. Ethylene turns to be both a stronger (Dessy) and a weaker (Applequist) acid than benzene (Table 10). The MSAD scale gives preference to the Dessy acidities.

The MSAD methane acidity is pKa = 40. The same value was proposed by Morton[52] in 1944 and, later on, by Pearson and Dillon[34]. The pKa obtained by Kosower[85] is 47 while Schwarzenback[86] and Bell[87] obtain a value for pKa(CH_4) of 58. The pKa obtained by polarography is 57 (see below). Maksic and Eckert-Maksic[88] calculated some CH-acidities as a function of s-contribution in the C-H bond under ionisation; their pKa for methane is 50. Streitwieser calculated pKa(CH_4) to be 48[89].

Consequently, the MSAD pKa values of alkanes are minimal and the real acidities are, probably, ten to fifteen orders lower[15,90 , 91].

3. Acidity in Dimethylsulphoxide

Dilute solutions of alkali hydroxides and alkoxides in dimethylsulphoxide or

its mixtures with water and alcohols are so-called highly basic media. Such media are defined by Bowden[92] as media that are capable of ionising acids to a greater extent than are 0.1 M aqueous solutions of alkali hydroxides. Dimethylsulphoxide (DMSO) is a convenient solvent for a study of the acid ionisation of weak acids such as diphenylmethane.

Unlike many dipolar aprotic solvents, DMSO is stable in the presence of its conjugate base, the dimsyl anion $CH_3SOCH_2^-$, [43]. Consequently, CH-acids dissolved in DMSO may be titrated by potassium dimsyl. Kolthoff and Reddy[94] showed that a glass electrode may be used in pure DMSO. Ritchie and Uschold [95 97] employed potentiometric titration in pure DMSO to titrate CH-acids.

Another method described by Hammett[99] utilizes the function H-,. The H_ acidity scale was devised for aqueous and alcohol solutions of DMSO[100-102], then extended to almost pure DMSO[103]. The acidity scale in DMSO is shown in Table 12; it includes both the potentiometry data obtained in pure DMSO and the data obtained via the H_ function in DMSO containing water or alcohol,

$$H_- = pKa - lg ([RH] / [R^-])$$

where pKa is the negative logarithm of the dissociation constant of the indicator RH in the standard solution (e.g., in water). Acidities of alcohols in DMSO may be arranged as follows[97 104].

MeOH (pKa 27) > EtOH (27,4) > n-PrOH (28) > t-BuOH (29,2) > H_2O (>29)

These data are very important because they allow one to estimate relative acidities of alcohols in the media in which specific hydrogen-bond solvation is hindered. Alcohol acidities in DMSO are comparable with the triphenylmethane acidity (Table 12), which fits in with the data on ionisation in the gas phase (Section I of this Chapter). The high activity displayed by alkoxide ions in DMSO is used in synthesis extensively[105].

By comparing CH-acidities in DMSO with those in water it is seen that the quantity ΔpKa = pKa (in H_2O) - pKa (in DMSO) is in some cases negative, in some cases positive and varies in the region +5 to -14 (Table 13). Consequently, there is no correlation whatever between acidities in water and those in DMSO. This may be due to not only the difference in the carbanion solvation but also to a difference in solvation of neutral molecules of CH-acids.

Ritchie[104] queried whether the function H- might not be a measure of CH-acidity. He argued that potentiometric results obtained with a glass electrode (containing mercury) disagree with the results obtained via the H- function, for instance,

	pKa (via H-)	pKa (potentiometrically)
fluorene	21.0[102]	20.5[90]
2-methoxyfluorene	22.4[69]	21.1[90]
9-methylfluorene	21.8[69]	19.7[98]
9-phenylfluorene	18.6[102]	16.4[98]
9-carbomethoxyfluorene	12.9[102]	10.3[98]
9-cyanofluorene	11.4[102]	8.4[90]

The acidity function method is discussed in more detail below.

TABLE 12

CH-Acidities in DMSO*

Acid	pKa	Acid	pKa
9-Cyanofluorene	8.4	$PhCH_2CN$	21.3**
9-Carbomethoxyfluorene	10.3	$(PhCH_2)_2SO_2$	21.4*** footnote[a]
Fluoradene	10.5	$PhCOCH_2CH_3$	21.8*** footnote[a]
$CH_2(CN)_2$	11.0	$PhCOCH_3$	22.5****
$C_6H_5COCH_2COCH_3$	12.1	1,1,3-Triphenylpropene	23.1
$(4\text{-}NO_2C_6H_4)_3CH$	12.2	$PhCOCH(CH_3)_2$	23.6*** footnote[a]
HCN	12.9	CH_3COCH_3	24.2*** footnote[a]
$CH_3COCH_2COCH_3$	13.4	9-Phenylxanthene	25.5
CH_3NO_2	15.1****	$PhC\equiv CH$	26.1*** footnote[a]
	15.9	$PhCH_2SOCH_3$	26.3*** footnote[a]
	16.6*****	$PhSO_2CH_3$	
9-Phenylfluorene	16.4	p-Biphenylyldiphenylmethane	26.9
Indene	18.5	$PhCH_3$	28.3
1,2-Benzofluorene	17.9	CH_3CN	29.1
9-Methylfluorene	19.7	Ph_2CH_2	30.0
4,5-Methylenephenanthrene	20.0	CH_3SOCH_3	33.1
Fluorene	20.5		

* Based mainly on ref. 104 ** Ref. 103
*** Ref. 108 **** Ref. 91 ***** Ref. 106

[a] The values in ref. 108 are 0.4 pKa units higher because they were obtained with p-biphenylyldiphenylmethane as standard acid with pKa of 27.3[103] rather than 26.9[104]

The acidity constants found for an acid, RH, in a given solvent (superscript s)

$$K_a^s = \frac{a_{H^+}^s \; a_{R^-}^s}{a_{RH}^s}$$

and in a reference solvent (superscript o)

$$K_a^o = \frac{a_{H^+}^o \; a_{R^-}^o}{a_{RH}^o}$$

define the proton activity in these solvents,

$$-\log a^{s}_{H^+} = pK^{s}_{a} + \log \frac{a^{s}_{R^-}}{a^{s}_{RH}}$$

$$-\log a^{o}_{H^+} = pK^{o}_{a} + \log \frac{a^{o}_{R^-}}{a^{o}_{RH}}$$

where a are activities of the respective species in the standard reference solvent (o) and in the solvent under investigation (s).

TABLE 13

Acidities in Water Compared with those in DMSO

Acid	pKa in H_2O, Table 4	pKa in DMSO Table 12	ΔpKa
$CH_2(COCH_3)_2$	8.9	13.4	-4.5
HCN	9.3	12.9	-3.6
CH_3NO_2	10.2	15.9(16.9)	-5.7
$CH_2(CN)_2$	11.2	11.0	+0.2
H_2O	15.7	29	-14
$(4\text{-}NO_2C_6H_4)_3CH$	17.4 (alcohol)	12.2	+5

These equations are the basis of the indicator method of measuring pH in aqueous solutions (a_{R^-} and a_{RH} are the activities of the ion and molecular forms of the indicator). The method is based on estimating the concentrations of basic and acid forms of the indicator via the colour of the solution, and thus the acidity of the medium is found. A correct application of the method (in the absence of oxidants or reducing agents, in the presence of buffers, with corrections made for ion strength) leads to accurate pH values. However, errors inherent in the standardisation of pH (as in potentiometric methods) are possible.

The standardisation may be made as follows,

$$-\log a^{s}_{H^+} + \log a^{o}_{H^+} = pK^{s}_{a} - pK^{o}_{a} + \log \frac{a^{s}_{R^-}}{a^{s}_{RH}} - \log \frac{a^{o}_{R^-}}{a^{o}_{RH}} \qquad (1)$$

$$= pK^{s}_{a} - pK^{o}_{a} + \log \frac{{}^{o}\gamma^{s}_{R^-}}{{}^{o}\gamma^{s}_{RH}}$$

where ${}^{o}\gamma^{s}_{R^-}$ and ${}^{o}\gamma^{s}_{RH}$ are degenerate activity coefficients that characterise the change in chemical potential on going from an infinitely diluted solution of R and RH in the experimental solvent under investigation s to the infinitely diluted solution in the standard reference solvent o.

The latter expression may be transformed to give,

$$pK_a^s - \log \frac{a_{R^-}^o}{a_{RH}^o} = -\log a_{H^+}^s + \log \frac{{}^o\gamma_{RH}^s}{{}^o\gamma_{R^-}^s} = H_- \qquad (2)$$

where H_- is the acidity function. The symbol $^-$ (in R^-) means that the indicator is a non-charged acid (RH) related with a negatively charged base. (The Hammett H_o function describes a non-charged base as an indicator whose conjugate acid is a positively charged ion).

At the half-neutralisation point we have $\log a_{R^-}^o/a_{RH}^o = 0$, hence the function H_- gives a correct pKa value only when $({}^o\gamma_{RH}^s/{}^o\gamma_{R^-}^s) = 1$. In other words, the assumption that H_- is a measure of absolute activity ($\log a_{H^+}^s$) of the lyonium ions, SH^+, referred to a standard (e.g., aqueous) solution of protons holds only if the solvent effects on the carbanion and on the neutral CH-acid molecule are identical.

But all the available data demonstrate that this is not so. A significant drawback of the Hammett method is the necessity to use a set of indicators for measuring the acidity. On the other hand, the method is very simple and does not necessitate the measurement of potentials, so there are no complications due to interface potential drops. This method is, therefore, very attractive and finds application in various branches of chemistry.

TABLE 14

The Function H- for a 0.01M Solution of Me_4NOH in DMSO-water[109]

DMSO molar percentage	H-	DMSO molar percentage	H-	DMSO molar percentage	H-
10.32	13.17	55.95	18.08	90.07	21.98
15.20	13.88	58.56	18.34	92.47	22.45
20.18	14.49	62.27	18.72	94.74	23.01
23.57	14.86	64.20	18.92	95.77	23.32
26.95	15.22	69.09	19.41	96.21	23.48
30.11	15.54	71.35	19.65	97.13	23.88
33.42	15.87	73.69	19.90	97.89	24.25
36.79	16.17	76.12	20.14	98.29	24.50
39.86	16.48	78.36	20.38	98.71	24.84
43.27	16.83	80.78	20.68	99.14	25.30
46.54	17.12	83.14	20.97	99.59	26.19
49.59	17.42	85.46	21.25		
52.55	17.73	88.79	21.61		

The H- acidity scale for DMSO/water mixtures is given in Table 14. The plot in Fig. 1 shows that the curve of H_- as a function of DMSO concentration in water rises more and more steeply as the DMSO content approaches 100%. The H-value is 29.5 for a 0.01 M potassium hydroxide in pure DMSO, and it is approximately three units lower in the presence of just 3% (mol/mol) water.

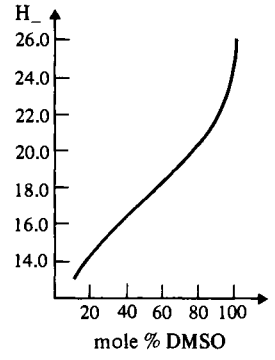


Fig. 1. H_ vs. mole percentage of dimethylsulphoxide in aqueous domethylsulphoxide 0.01 M tetramethylammonium hydroxide.

Steiner[110] determined the indicator ratio as a function of the concentration of a hydroxyl-containing solvent (MeOH, EtOH, t-BuOH, 1,2-butanediol, water) and the conjugate base concentration in DMSO. He studued 2,4-dinitroaniline (14.7), 1,2-benzofluorene (17.9), indene (18.3), p-nitroaniline (18.4), fluorene (20.2), 1,1,3-triphenylpropene (23.1), 9-phenylxanthene (25.5), and triphenylmethane (28.3), (H values in parentheses). The quantity pK_R as a function of the logarithmic concentration of the hydroxyl-containing solvent in DMSO was written as follows,

$$pK_R' = \log\frac{[RO^-]t}{[ROH]t} + pK_{Ind} + \log\frac{[Ind^-]}{[HInd]} = -\log\frac{[RO^-]t}{[ROH]t} + H_-$$

where $[RO^-]t$ and $[ROH]t$ are stoichiometric concentrations of the alkoxyl ion and the hydroxyl-containing compound, pK_{ind} is the H_ value at the half-neutralisation point and $[Ind^-]$and [HInd] are concentrations of the conjugate base and the acid form, of the indicator.

The pK_R' vs.ROH concentration plots have the characteristic shape of "curves with saturation": pK_R' was almost constant for low concentrations of ROH. If the H_ function is valid for the indicators under discussion, then the patterns obtained may be assumed to reflect the formation of mono-, di-, tri-, and tetra-solvated anions of the hydroxyl components.

In this way formation constants (K_{form}) of the mono-solvates were estimated by Steiner[110].

Solvate	K_{form} in DMSO
CH_3O^- .... $HOCH_3$	$10^{3.9}$
$C_2H_5O^-$ .... HOC_2H_5	$10^{3.6}$
$(CH_3)_3CO^-$.. $HOC(CH_3)_3$	$10^{2.5}$

With sodium and lithium alkoxides, a significant effect of counterions was found on pK_R values. For the methylate anion, the ion-pair effect was observed even at millimolar concentrations of potassium ion. Formation constants of ion-pairs were as follows[110]

$CH_3O^-Li^+$	10^9
$CH_3O^-Na^+$	10^5
$CH_3O^-K^+$	$10^{2.5}$
$(CH_3)_3CO^-Li^+$	$10^{7.6}$
$(CH_3)_3CO^-Na^+$	$10^{5.4}$

Ion aggregates of a higher order were, probably, also formed. Thus, H_- in water/DMSO at 0.002 to 0.01 M water concentrations was found to be independent of the concentration of potassium hydroxide in the range 0.002 to 0.025 M.

Consequently, limiting values of $pK_R^{\prime}$ are observed at lower concentrations of hydroxyl-containing solvents. Probably, the limiting values are a measure of the ionisation constants of hydroxyl-containing compounds referred to the standard state in pure DMSO[104].

Application of H_- in a study of rates and mechanisms of proton transfer, kinetic isotope effect of hydrogen, and other reactions[48] will be dealt with in the ensuing Chapters.

To conclude, it should be emphasised that, however attractive, the function H_- (and similar functions) may be, they do not reflect the real acidity of non-aqueous solutions since solvent effects on the charged and non-charged forms of the indicator differ almost in all the cases examined to date.

4. Acidity in Dimethoxyethane

Recently Shatenshtein et al.[169] have proposed an acidity scale in dimethoxyethane (Table 15). It is based on redistribution equilibria occuring between CH-acids and organolithium or -caesium compounds. The equilibration was instantaneous with the organocaesium compounds but took a day or more with the organolithium compounds.

As a rule, λ_{max} of the anions studied underwent a hypsochromous shift on going from the lithium to the caesium salts. In Smid's terms[170], RLi^+ are solvent-separated ion-pairs whereas R^-Cs^+ are intimate ion-pairs. However, the bathochromic shift was observed for indene. Consequently, both the lithium and caesium salts of indene are intimate ion-pairs.

The dissociation constants ($x10^5$ 1/mole) of ion-pairs are as follows: 1,1,3,3,-tetra-phenylpropene, 3.5(Li^+), 2.4 (Cs^+); benzanthrene, 1.4(Li^+), 0.5 (Cs^+).

The general conclusion to be reached in the discussion of methods of equilibrium CH-acidity measurement discussed so far is that equilibrium acidities found in apolar solvents or solvents of low polarity, such as methane, ether, benzene, dimethoxyethane (and DMSO for OH-acids) reflect ion-pair ionisation.

5. Polarographic Scale of Acidity

The polarographic approach to CH-acidity is based on the polarography of organomercury compounds. Indeed, the polarity of the C-Hg bond closely resembles that of the C-H bond and, on the other hand, almost all organomercurials of the type R_2Hg are polarographically active regardless of the structure of the organic group R. Reduction potentials of organomercury

compounds on the mercury cathode are strongly dependent on the nature of the groups bonded with the metal. Dialkylmercury compounds are the most difficult to reduce. The range of reduction potential observed for organomercury compounds is very wide, the half-wave potentials of dimethylmercury and of the mercury (II) salt of α-hydrohexafluoroisobutyronitrile differ by more than three volts, consequently, even the slightest structural change in the organic group will lead to appreciable changes in the reduction potential. This opens wide horizons for a study of structure as a function of electrochemical properties in organomercury compounds. This strong dependence of reduction potential on structure is not observed in other σ-organometallic compounds (tin, lead, magnesium, thallium, etc.).

TABLE 15

Equilibrium Acidity Scale in Dimethoxyethane[169]

Compound	pKa	
	Li^+(a)	Cs^+(b)
9-Phenylfluorene	(18.5)	17.5
Indene	20.3	19.0
Benzanthrene	20.6	20.3
9-Benzylfluorene	21.9	20.9
9-Dimethylaminofluorene	23.3	22.1
Fluorene	23.3	22.0
9-Isopropylfluorene	23.7	22.5
Phenylacetylene	23.7	26.9
9-tert-Butylfluorene	24.8	23.7
1,1,3,3-Tetraphenylpropene	25.8	(25.8)
9-Phenylxanthene	27.7	27.7
p-Biphenylyldiphenylmethane	29.1	29.3
9,10-Dihydroanthracene	30.2	29.7

(a) 9-Phenylfluorene as a standard (pKa 18.5 in aqueous sulfolane).

(b) 1,1,3,3-Tetraphenylpropene as a standard.

The polarographic method has the advantage that it may be used to estimate acidities in a very wide range of pKa values in any polar solvent even if the solvent is more 'acidic' than is the CH-acid under study. It is based on a correlation between the electrochemical reduction parameters of the organomercury compound and the pKa values of the respective acids RH.

Streitwieser and Perrin[111] were the first to attempt a polarographic estimation of carbanion stabilities. They measured the reduction potentials for benzyl chlorides and polycyclic arylmethyl chlorides in dimethylformamide.

$$ArCH_2Cl + 2e^- \xrightarrow{E_{\frac{1}{2}}} ArCH_2^- + Cl^-$$

If the transition state were close to the carbanion, $ArCH_2^-$, it would be expected that a correlation would exist between the reduction potentials of the organic chloro compounds and the carbanion stabilities (pKa's of the CH-acids). However, as the slow step in the reactions studied by Streitwieser

and Perrin[111] was transfer of the first electron involving a radical-type transition state, the correlation was not satisfactory.

Dessy et al.[84] employed the half-wave potentials of organomercury salts as a measure of relative CH-acidities. However, this attempt was not successful either.

$$RHgX \xrightarrow[\text{1st wave}]{} RHg. \longrightarrow \tfrac{1}{2}(RHgHgR) \xrightarrow[\text{2nd wave}]{E_{\frac{1}{2}}} R^- + Hg$$

The method of Reutov et al[112 114] is based on the measurement of electrochemical reduction parameters for symmetrical organomercury compounds.

$$R_2Hg + 2e^- \xrightarrow{\alpha n_a E_{\frac{1}{2}}} 2\,R^- + Hg$$

An essential feature of this method is that it includes not only the half-wave potential, $E_{\frac{1}{2}}$, but also the electrochemical transfer coefficient αn_a which varies with the organometallic substrate[112 113]. If it is assumed[114] that the electroreduction mechanism is the same over a wide range of organomercury compounds, i.e. that the C-Hg bond decomposition occurs in the transition state and the organic group R acquires a partial negative charge, then the acidities of CH-acids may be easily derived from the ability of the respective organomercury compound to undergo electrochemical reduction.

The following three processes may be interrelated:

(i) acid dissociation of the CH-acid,

$$RH \overset{Ka}{\rightleftharpoons} R^- + H^+ \qquad (1)$$

(ii) dissociation of the organomercury compound.

$$R_2Hg \overset{1/Km}{\rightleftharpoons} 2R^- + Hg^{2+} \qquad (2)$$

(iii) and electrochemical reduction of the organomercury compound

$$R_2Hg + 2e^- \longrightarrow 2R^- + Hg \qquad (3)$$

The equilibrium constants Ka and Km in equations (1) and (2) describe carbanion stabilities in the medium containing proton donors or mercury cation donors, respectively.

To express CH-acidities through electrochemical reduction parameters of the mercury salts, Reutov et al[112 113] assume that the carbanion affinity for the proton is a linear function of the affinity for the mercury cation (equation (3)). Recently, indirect NMR evidence[115] has been obtained which is in favour of this assumption. Scheffold[116] who studied mercury-proton couplings in complexes of the methylmercury cation (CH_3Hg^+) with various anions (X^-), showed that the couplings vary with the logarithmic stability constants of the complexes.

$$CH_3Hg^+ + X^- \overset{K_m'}{\rightleftharpoons} CH_3HgX; \qquad K_m' = \frac{[CH_3HgX]}{[CH_3Hg^+][X^-]}$$

Consequently, NMR spectra allow one to estimate the strength of the bond of

CH_3Hg^+ with X^-. The Scheffold[116] correlation embraces anions containing various donor atoms such as oxygen, sulphur, nitrogen, halogens and, last but not least, carbon (CN^-anion). Therefore, this correlation may help to estimate the stability constants of methylmercury cation complexes with carbanions, in particular, alkyl anions.

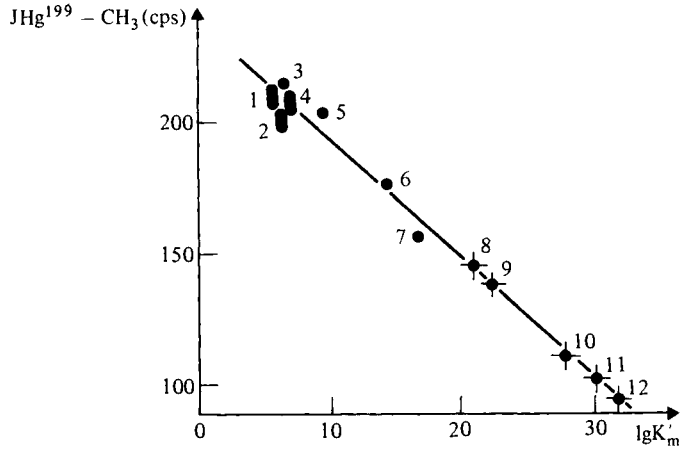


Fig. 2. J Methyl-proton couplings $J(^{199}Hg\text{-}CH_3)$ for CH_3HgX vs. pKm. Points: X = Cl (1), SCN (2), $OCOCH_3$ (3), Br (4), OH (5), CN (6), $SHgCH_3$ (7), C≡CH (8), CF_3 (9), $CH{=}CH_2$ (10), CH_3 (11), C_2H_5 (12).

Figure 2 shows methyl-proton couplings ($J(^{199}Hg\text{-}CH_3)$) vs. log K_m', the X^- affinity for the methylmercury cation. If this is extrapolated to lower J's (the J sign seems to be invariable[117]), it is possible to estimate logKm' values for $HC{\equiv}C^-$, $\overline{C}F_3$, $H_2C{=}\overline{C}H$, $\overline{C}H_3$, $C_2\overline{H}_5$. This series includes compounds in which hybridisation of the negatively charged carbon orbital does not essentially differ from hybridisation of the orbital in the CH-acid or the mercury salt, i.e., rehybridisation effects involved in ionisation via equations (1) and (2) are insignificant. That is probably why the correlation is satisfactory (cf. also Chapter II).

TABLE 16

Affinity of Carbanions for the Methylmercury Cation[115]

Anion	lgK_m'	Anion	lgK_m'
1. CN^-	(14.2)	4. $CH_2{=}\overline{C}H$	28
2. $HC{\equiv}C^-$	21	5. $\overline{C}H_3$	30*
3. $\overline{C}F_3$	22	6. $C_2\overline{H}_5$	31.5

* lgK_m' = 30, Pearson[118].

The log K_m' values obtained (Table 16) correlate fairly well with Cram pKa's

of the respective hydrocarbons, (Fig. 3). The equation relating log K_m' with pKa is as follows

$$\log K_m' = 0.6\ pKa\ (MSAD) + const$$

Of course, this relationship may or may not hold, for in a wide range of anions since the proton is a hard acid whereas mercury-containing cations are soft acids[118]. With similar donor atoms in the Lewis base, however, relations of the following type are quite probable.

$$RH \underset{}{\overset{Ka}{\rightleftharpoons}} R^- + H^+$$

Indeed, it has been shown[119] that for methylmercury cation the logKm patterns as a function of the pKa of the donor species are straight lines whose slopes increase across the series of O-donors < N-donors < P-donors.< S donors. Also, many parallels were found between donor affinity for proton and the donor affinity for other Lewis acids (see the reviews[120 121]), whereas the HSAB concept[18] concentrates just on the facts that disagree with the regularities mentioned. Probably, the two points of view are not incompatible[122], viz., there is quite enough data in favour of both modus generalis and differentia specifica in acid-base reactions.

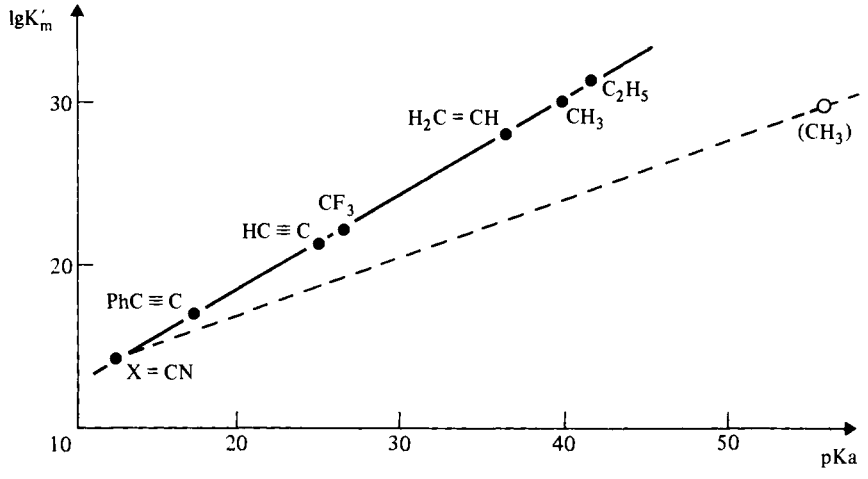


Fig. 3. pK_m' vs. pKa for carbanions.

Consequently, let us assume that carbanion affinity for the proton is linearly dependent on the carbanion affinity for the cation Hg^{2+}, namely

$$\Delta \ln K_m = A \cdot \Delta pKa \qquad (1)$$

where A is a constant, $\Delta \ln K_m$ is the difference between $\ln K_m$'s of two

organomercury compounds, ΔpKa is the difference between pKa's of the respective CH-acids.

For an equilibrium reduction of an organomercury compound (R_2Hg) we have.

$$\Delta G^o = -RT\ln K_m + \Delta G(Hg^o/Hg^{2+})$$

where $\Delta G(Hg^o/Hg^{2+})$ is the Hg^o/Hg^{2+} redox potential. By comparing two organomercury compounds we obtain the following equation.

$$-\Delta\Delta G^o = RT\cdot\Delta\ln K_m \qquad (2)$$

Equations (1) and (2) give (3)

$$-\Delta\Delta G^o = RT\cdot A\cdot\Delta pKa \qquad (3)$$

The reduction rates of the organomercury compounds should be compared at the same potential E. Each of the compounds has its overvoltage, η,

$$\eta = E - E^o \qquad (4)$$

where E^o is the equilibrium potential for a given organomercury compound. Equations (3) and (4) give the following expression for the difference between overvoltages of two organomercury compounds.

$$\Delta\eta = -\Delta E^o = \frac{\Delta\Delta G^o}{F} = \frac{RT\cdot A}{F}\Delta pKa \qquad (5)$$

The electrochemical reduction constant may be expressed through overvoltage as follows,

$$\ln k_e = \ln k_e^o - \frac{\alpha n_a F}{RT}\eta \qquad (6)$$

where k_e^o is the electrochemical reduction constant at the equilibrium potential, n_a is the number of electrons participating in the slow stage and α is the electrochemical transfer coefficient. This parameter may be interpreted similarly to the Brönsted proton transfer coefficient. Variation of potential corresponds to a shift in the reduced/oxidised forms equilibrium while variation in pKa corresponds to a shift in the protolytical equilibrium. The quantity α reflects the extent of the forward reaction as a function of potential. It may be easily found from slopes of polarographic waves. Equation (6) assumes that the transfer coefficient is independent of overvoltage.

If α depends on overvoltage[124, 125], then for a value of $n_a = 1$, equation (6) may be rewritten in the following form.

$$\ln k_e = \ln k_e^o - \frac{F}{RT}\int_o^\eta \alpha d\eta \qquad (7)$$

For a pair of organomercury compounds the rate difference at the same potential, e.g. at E = 0 relative to a reference electrode, is expressed as follows:

$$\Delta \ln k_e = \Delta \ln k_e^o - \frac{F}{RT}\int_{\eta_1}^{\eta_2} \alpha d\eta$$

whence

$$\Delta \ln k_e = \Delta \ln k_e^o - \frac{\alpha_e F}{RT} \eta \qquad (8)$$

where α_e is the average transfer coefficient at the interval η_1-η_2.

Combination of equations (5) and (8) gives the following relationship

$$\Delta \ln k_e = \Delta \ln k_e^o - \alpha_e A.\Delta pKa \qquad (9)$$

Now, if it is assumed that the organomercury reduction rates at equilibrium potential are proportional to pKa (RH) and that α_e is constant at the overvoltage interval considered, then equation (9) leads to the following relationship

$$\Delta \ln k_e = -\rho'.\Delta pKa \qquad (10)$$

Consequently, by measuring the electrochemical reduction constant for a series of organomercury compounds at the same potential, it is possible using equation (10) to calculate CH-acidities. However, to include all the possible organic substituents (R) in organomercury compounds of the type R_2Hg, the measurement would have to embrace an interval of three volts or wider, so it is impossible. On the other hand, the rate constants may be roughly estimated via the Koutecki-Delahay equation[126] that may be written as follows for a constant dropping period of the mercury electrode provided that the nature of the group R in R_2Hg has little influence on the diffusion coefficient of the organomercury compound.

$$\frac{\alpha n_a F}{RT} E_{\frac{1}{2}} = \ln k_{E=0} + \text{const} \qquad (11)$$

where $k_{E=0}$ is the electron transfer rate constant at E = 0 with respect to a reference electrode and α is the polarographical transfer coefficient at the half-wave potential ($E_{\frac{1}{2}}$).

Equations (10) and (11) lead to the following relationship

$$\Delta(\alpha n_a E_{\frac{1}{2}}) = \rho \cdot \Delta pKa \qquad (12)$$

where ρ is an empirical constant which cannot be calculated and must be experimentally determined.

Using equation (12) it is possible to estimate pKa's for many CH-acids whose acidities were not known before. This resulted in the polarographic scale embracing acids differing by more than fifty pKa units in their acidity[127-134] as is shown in Table 17. The solvent used in the determination of these pKa values was anhydrous dimethylformamide (DMF). The values of $E_{\frac{1}{2}}$ and αn_a were found from the Heyrovsky plots. To find the constant (equation 12) the following acids were used: (i) hydrogen cyanide whose pKa of 12 was found by potentiometric titration in DMF, (ii) phenylacetylene, cyclopentadiene, toluene, and benzene, whose pKa's were taken from the Cram MSAD scale, and

(iii) methyl acetate whose pKa was assumed to be 24[2]. The value of $\rho = d(\alpha n_a E_{1/2})/dpKa$ was -55 mV. Following this, pKa values of other acids were found.

TABLE 17

Polarographic Scale of Acidity

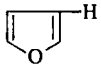
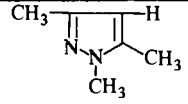
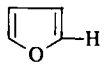
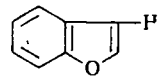
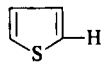
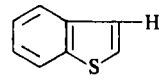
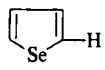
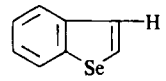
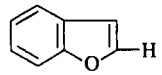
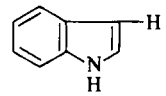
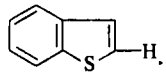
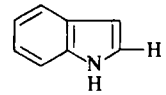
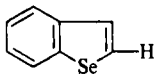
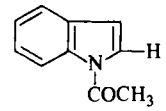
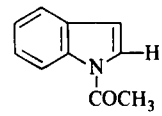
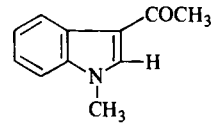
Compound	pKa	Compound	pKa
1. Hydrocarbons and their derivatives			
1. $(CH_3)_2CH-H$	60±10	11. $CH_2=CH-H$	36±5
2. $(CF_3)_2CH-H$	22±3	12. $CHCl=CH-H$	31±4
3. $(CF_3)_2CFH$	22±2	13. $CF_2=CF-H$	20±4
4. CH_3-H	57±8	14. $PhCH_2-H$	35±5
5. $PhSO_2CH_2-H$	24±2	15. $p-CF_3C_6H_4CH_2-H$	28±3
6. CH_3OOCCH_2-H	24±2	16. $C_6F_5CH_2-H$	25±3
7. $EtOOCCH(Ph)-H$	17±2		
8. C_6H_5-H	37±5	17. $PhC\equiv C-H$	18.5±3
9. C_6Cl_5-H	30±4	18. $cyclo-C_5H_5-H$	15.5±1
10. C_6F_5-H	23±3	19. $N\equiv C-H$	12±1
2. Heterocyclic compounds			
20. 	37±5	24. 	38±5
21. 	36±5	25. 	37±5
22. 	35±5	26. 	36±5
23, 	35±5	27. 	36±5
28. 	35±5	31. 	38
29. 	35±5	32. 	36±5
30. 	34±5	33. 	34±4

TABLE 17-*continued*

Compound	pKa	Compound	pKa
		34. 	33±4
		35. 	33±4
3. Esters of unsaturated acids			
36. $CH_3CH=C(COOCH_3)H$	32 ± 4	38. $p-BrC_6H_4CH=C(COOCH_3)H$	26 ± 3
37. $PhCH=C(COOCH_3)H$	23 ± 3	39. $p-CH_3OC_6H_4CH=C(COOCH_3)H$	29 ± 3
4. Carboranes			
40. para-Carborane	33±3	42. ortho-Carborane	18±2
41. meta-Carborane	21±3		
5. Haloforms			
43. CF_3-H	26.5±2	45. CB 3-H	9±1
44. CCl_3-H	15±1		
6. Halogenated carboxylic esters			
46. H-CF_2COOEt	25±2	49. H-CH(CF_3)COOEt	16±1
47. H-CHFCOOEt	21±2	50. H-CF(CF_3)COOEt	14±1
48. H-CFClCOOEt	18±2	51. H-C(CF_3)$_2$COOEt	14±1
7. CH-acids with high acidities			
52. $(CF_3)_3C$-H	7±1	54. $(CF_3)_2(CN)C$-H	0±1
53. $F(NO_2)_2C$-H	3±1		

The plots in Fig. 4 show that $\alpha n_a E_{\frac{1}{2}}$ varies smoothly with pKa whereas the relationship between pKa and half-wave potential is more erratic. This may be due to the fact that in irreversible processes, where αn_a varies in going from one compound to another, $E_{\frac{1}{2}}$ does not directly reflect the inherent redox properties of the system. In this connection it is interesting to note that recent work by Denisovich and Gubin[172] indicate that CH-acidities (pKa's) correlate with the half-wave potentials of organomercury compounds better than with $\alpha n_a E_{\frac{1}{2}}$. The conclusion is based on the observation that the

correlation coefficient (r = 0.966) calculated with six experimental points for $E_{1/2}(R_2Hg)$ vs. pKa(RH) is a little better than the coefficient (r =0.961) calculated for $\alpha n_a E_{1/2}$ vs. pKa. It should be emphasised that if an electrochemical process is irreversible and αn_a varies significantly in going from one compound to another, then the half-wave potential cannot be a characteristic of the effect of structure on the electrochemical properties. It is just a potential at which the electroreduction rate is equal to the diffusion rate, and is hardly interpretable otherwise.

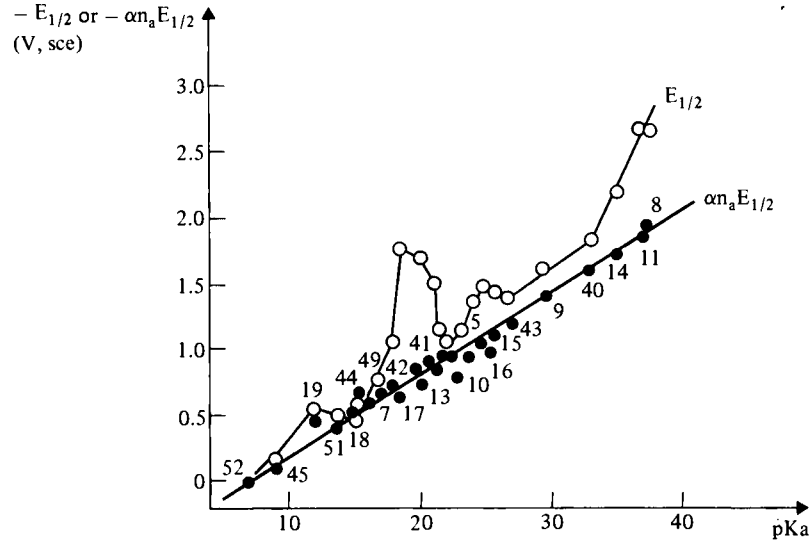


Fig. 4. The plots of $\alpha n_a E_{\frac{1}{2}}$ and $E_{\frac{1}{2}}$ vs. pKa of RH.
The figures correspond to compounds listed in Table 17.

The accuracy of pKa values obtained polarographically depends on various factors, (i) the accuracy of the half-wave potential, (ii) the accuracy of the αn_a calculation, (iii) the potential at which the reduction rates are compared, (iv) the effect of complex-forming agents and of solvents on the half-wave potential, and (v) the selection of reference points for the calculation of the empirical constant ρ. The effect on accuracy of each of these factors is discussed below.

(i) Modern apparatus is capable of measuring potentials accurately to hundreths of millivolt. This error is too low to affect the pKa value calculated using equation (12). The error contributed by the difference between the diffusion coefficients of the organomercury compounds is not high. The dropping period may be made practically constant by applying forced dropping.

(ii) The situation with αn_a found from the Heyrovsky plot is much worse. A conventional estimate for the error is 10%, an order higher than with $E_{\frac{1}{2}}$.

(iii) The dependence of $\ln k_e$ on electrode potential (on overvoltage) is shown in Fig. 5. It is clear that the error in $\ln k_e$ depends on the potential $E_{\frac{1}{2}}$ at which the reduction rates of the organomercury compound are compared. Thus, the quantity $\alpha n_a F(E_{\frac{1}{2}} - E')/RT$ found through linear extrapolation to E' of the tangent at the point E (Fig. 5) does not reflect the real value of $\ln k_e$, and the deviation becomes higher the more negative the reduction potential.

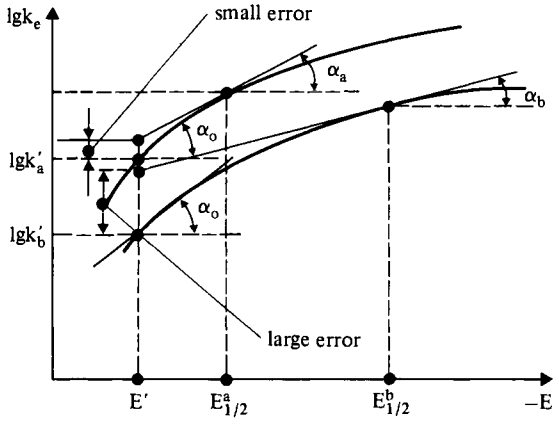


Fig. 5. $\ln k_e$ vs. electrode potential for two organomercury compounds.

(iv) Complexing agents in the solution may affect the half-wave potential considerably. In the system anhydrous DMF plus tetrabutylammoniumperchlorate the only complexing agent is the solvent. Complex formation of most of symmetrical organomercury compounds with DMF can hardly be significant, so the complexation effect on $E_{\frac{1}{2}}$ may be neglected.

(v) The polarographic scale is, in all probability, an extended MSAD scale since the reference points for calculating the constant ρ (see equation 12) are pKa's from the latter scale. Consequently, the accuracy of the polarographic scale depends on the accuracy of the MSAD scale which is about $\pm$0.5 pKa units[2].

Thus, error in pKa estimation is mainly due to factors (ii) and (iii) viz. accuracy of αn_a calculation and the potential at which reduction rates are compared. The plot in Fig. 5 helps to estimate the inaccuracy inherent in non-linearity of the $\ln k_e$ vs. potential (overvoltage). Thus, if a compound is reduced at -2 volts and if αn_a is unity at potentials of 0.5V or less[135] then at the maximal value of ρ of -1 (equation 10) the error in pKa will be 3-4 pKa units and the deviation will tend towards lower pKa's. Compounds reducing at these potentials correspond to CH-acidities of 30-35 pKa units.

The respective error in pKa will be 10%. For compounds reducing at more positive potentials, the error due to the factor (iii) will be lower whereas the error inherent in αn_a (factor (ii) measurements will remain unaffected.

A more involved analysis shows that the error in pKa is maximal when the compound reduces at very negative potentials and its αn_a value lies at the "middle" (0.4-0.6) range. This is because at lower α's the error in αn_a affects pKa only slightly whereas at higher α's the error due to the rate vs. potential non-linearity is lower. All these considerations are reflected in the results quoted in Table 17.

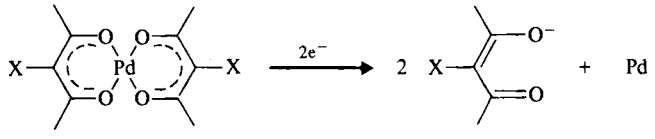
The polarographic method can be used to study a very wide range of pKa values. It can work with compounds containing base-sensitive groups and, also, with the relative stabilities of isomeric carbanions having isomerism in the charge position.

It should be emphasised that equation 12 holds only if C-Hg bond decomposition occurs in the electrolysis transition state and the potential is not affected by any following carbanion stabilisation process. Probably, some of the compounds placed at the end of Table 17 violate this restriction since their reduction may be to a considerable extent reversible.

$$(CBr_3)_2Hg \overset{2e^-}{\rightleftharpoons} Hg + 2\ CBr_3^- \xrightarrow{*)} 2\ CBr_2 + 2\ Br^-$$

*) The potential may be affected at this stage.

If the carbanion affinity for protons is a linear function of not only their affinity for the mercury cation but also their affinity for cations of other metals[122], then relationships similar to that shown in equation (12) should be observable in other organometallic compounds. Gubin et al[136] have found that equation (12) is valid for palladium acetylacetonate and Vlcek[137] has reported that cobalt acid pentaammoniate complexes also follow this relationship. The reduction patterns are shown below.



$$[Co(NH_3)_5X]^{n-} \xrightarrow{e^-} [Co(NH_3)_5]^{n-} + X^-$$

The plots in Figs. 6 and 7 demonstrate that the quantity $\alpha n_a E_{\frac{1}{2}}$ calculated for the palladium complexes correlates fairly well with the pKa's of the respective acetylacetonates while for the cobalt complexes there is a good correlation with the pKa's of the acids HX. As in the case of organomercury compounds, there is no linear dependence of pKa on $E_{\frac{1}{2}}$.

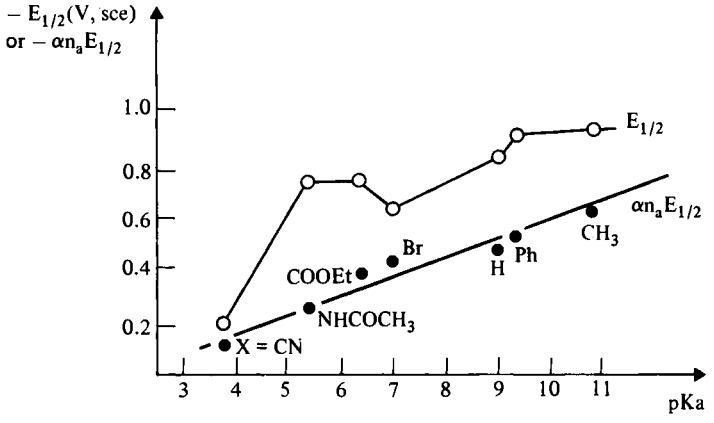


Fig. 6. $\alpha n_a E_{\frac{1}{2}}$ and $E_{\frac{1}{2}}$ vs. pKa for acetylacetonate complexes of palladium (II).

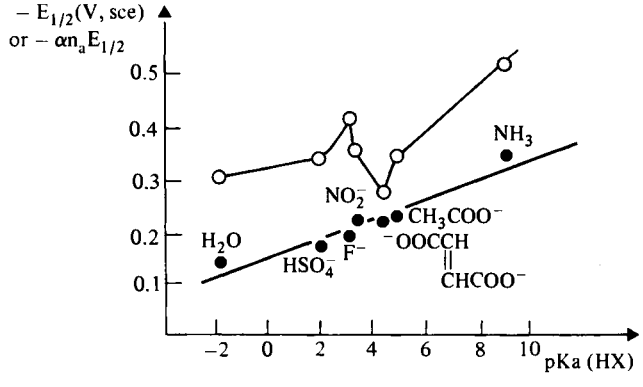


Fig. 7. $\alpha n_a E_{\frac{1}{2}}$ and $E_{\frac{1}{2}}$ vs. pKa(HX) for $[Co(NH_3)_5X]^{n+}$

However, in reversible systems containing a σ-bond group $Co-CH_3$, $Co-C_6H_5$, $Co-CH_2C_6H_5$, etc., the first half-wave potentials correlate fairly well with the pKa of the respective carbanions[138]. The same was found for pKa(RCOOH) and $E_{\frac{1}{2}}$ ($(RCOO)_2Hg$)) in methanol, DMF, and DMSO[139].

Table 18 compares the polarographic data with acidities found by other investigators. The data in the last column were obtained by various techniques, (trans-metalation equilibria, kinetic acidity, HMO calculations, indirect methods) in various solvents such as DMSO, dimethoxyethane, methanol, etc. Nevertheless, there is a good agreement between the pKa values.

TABLE 18

Polarographic Acidities Compared with Acidities obtained by Other Methods

Compound	pKa (polarographic)	pKa (other methods)	Ref. No.
1. CH_3-H	57±8	40	2,34,52
		47	58
		48	89,2
		50	88
		58	87
		84	157
2. $(CH_3)_2CH-H$	60±10	44	2
3. PhH	37±5	43	73
4. Thiophene	35±5	38.4	74
5. Benzothiophene	35±5	37.0	74
6. Benzofuran	35±5	36.8	74
7. para-Carborane	33±3	30.0	76,77
8. meta-Carborane	21±3	27.9	76,77
9. ortho-Carborane	18±2	23.3	76,77
10. $PhSO_2CH_2-H$	24±2	26.7	91
11. CF_3-H	26.5±2	28	140
12. CCl_3-H	15±1	15.5	140
13. CBr_3-H	9±1	13.7	140
14. HCN	12±1	12.9	140
15. $(CF_3)_3C-H$	7±1	11	141

The agreement is better when the polarographic measurements are made in the solvent in which the trans-metalation equilibrium was studied. Examples of this (Table 19) are the acidities of carboranes in dimethoxyethane with 0.1M tetrabutylammonium perchlorate as the supporting electrolyte. The calculated ρ value is -70mV.

The results in Table 19 demonstrate that the polarographic and equilibrium data agree quite well with each other, the quantites to be compared are the acidity incremants (ΔpKa) across the series rather than absolute pKa values as these depend on the reference employed.

TABLE 19

Carborane Acidities in Dimethoxyethane

Compound	ΔpKa	pKa (polarographic)	pKa Table 9	ΔpKa
o-Carborane	5	19±2	23,3	4,6
m-Carborane	2	24±3	27,9	2,1
p-Carborane		26±3	30,0	

6. The Electrochemical Method of Breslow.

Breslow and his co-workers[142-144] proposed an interesting electrochemical method for the measurement of the acidity of hydrocarbons for which direct acidity measurements are impossible. This indirect approach to the measurement of equilibrium acidity is based on the following reversible sequence.

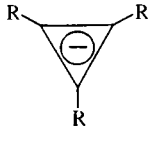
$$R\text{-}H \overset{1}{\rightleftharpoons} R\text{-}OH \overset{2}{\rightleftharpoons} R^{+} \overset{3}{\rightleftharpoons} R\cdot \overset{4}{\rightleftharpoons} R^{-}$$

The Breslow method is applicable to hydrocarbons with relatively stable carbenium ions and relatively unstable carbanions. Thermodynamical parameters for the steps 3 and 4 may be easily found via an electrochemical method such as measuring redox potentials for stepwise carbenium ion reduction to the carbanion. For the step 2, the thermodynamical parameters is the Deno pK_{R+} value[145] that describes the alcohol/carbonium equilibrium.

$$R - OH + H^{+} \overset{K_{R+}}{\rightleftharpoons} R^{+} + H_2O$$

Thermodynamical parameters for step 1 are difficult to obtain. Breslow[142-144] assumed that the difference between the heats of formation of a hydrocarbon and the respective alcohol varies only slightly in a series of related compounds. Breslow et al. started from McEven's pKa of 33 for triphenylmethane, calculated the step 1 parameter, and found the thermodynamic acidities for a number of substituted triphenylmethanes, cyclopropenes, and for cycloheptatriene. Their data are summaries in Table 20.

The high pKa's found for cyclopropenes are due to instability ("anti-aromaticity") of the respective anions.



The Breslow method is very attractive in that the low acidities that are measurable cannot be studied by any other technique.

TABLE 20

Breslow's CH-acidity Scale

Substituent X in $(4\text{-}XC_6H_4)_3CH$	pKa	Compound	pKa
H	(33)		
Chloro	32.3	Cycloheptatriene	36±3
H, H, CH_3O	33.1	Triphenylcyclopropene	51±4
Methoxy	33.4	Trimethylcyclopropene	62±5
Dimethylamino	34.7	Tri-n-propylcyclopropene	64±5
Methyl	33.6	Tri-tert-butylcyclo-	65±5
iso-Propyl	36.2	propene.	
tert-Butyl	35.2	Isobutane	70.7

7. Acidity Scale for Acidic Hydrocarbons

Fischer and Revicki[146] published a CH-acidity scale embracing the Kuhn hydrocarbons and polycyano hydrocarbons. The scale is shown in Table 21. In this Table pKa values are referred to the standard state in water via the function H_-.

TABLE 21

pKa Values of Acidic Hydrocarbons referred to Water as Standard Solvent.

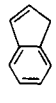
Compound[a]	pKa	Reference
1. Pentacyanocyclopentadiene	-10	24,147
2. Tetracyanocyclopentadiene	-10	24,147
3. $(NC)_2C=C[CH(CN)_2]_2$	-8.5	25
4. $(NC)_2C=C(CN)CH(CN)_2$	-8.5	25
5. $(NC)_2C=CHCH(CN)_2$	-8	25
6. $C(CN)_3H$	-5.1	25
7. $(NC)_2C=C(CN)CH=CH-CH=C(CN)CH(CN)_2$	-3.7	25
8. $(NC)_2C=C(CN)$ -  $-CH(CN)_2$	0.6[b]	25
9. $(DBBiphC=CH)_3CH$	5.9	38
10. $(DBBiphC=CH)_2CH_2$	8.2	146,148,149
11. DBBiphC=CHCHDBBiph	9.1	14-,148,149
12. $(BiphC=CH)_3CH$	9.4	146,148,149
13. $DBBiphC=CHCH_2CH=CBiph$	9.8	146,148,149
14. BiphC=CH-  =CH-CHBiph	10.0	146,148,149

TABLE 21 *continued*

Compound[a]	pKa	Reference
15. $(BiphC{=}CH)_2C{=}CHCHBiph$	10.4	146,148,149
16. $CH_2(CN)_2$	11.2	150
17. $(BiphC{=}CH)_2C{=}CH{-}CH{=}CH{-}CHBiph$	11.2	146,148,149
18. DBBiphCH-CH=CBiph	11.2	146,148,149
19. 9-Cyanofluorene	11.4[c)]	150
20. $BiphC{=}CH{-}CH_2{-}CH{=}CBiph$	11.8	146,148,149
21. BiphC=CH-CH=CH-CHBiph	12.2	146,148,149
22. PhenC=CH-CHPhen	13.6	146,148,149
23. PhenCH-CH=CBiph	13.6	146,148,149
24. Fluoradene	13.9	146,148,149
25. BiphC=C(Ph)CHBiph	14.0	146,148,149
26. BiphCH-CH=CPhen	14.0	146,148,149
27. BiphCH-CH=CBiph	14.3	146,148,149
28. BiphC=CH-CH(Ph)CH=CBiph	14.8	146,148,149
29. Cyclopentadiene	14-16	151
30. BiphCH-CH=CHPh	<15.5	146,148,149
31. 9-Phenyl-3,4,5,6-dibenzofluorene	15.9	146,148,149
32. 3,4,5,6-Dibenzofluorene	16.8	146,148,149
33. $BiphC{=}CH{-}CH_2Ph$	16.9	146,148,149
34. Biph $CH{-}CH{=}CPh_2$	17.1	146,148,149
35. $BiphC{=}CH{-}CHPh_2$	17.5	146,148,149
36. 9-Phenyl-1,2,7,8-dubenzofluorene	17.3	146,148,149
37. 1,2,7,8-Dibenzofluorene	17.5	146,148,149
38. 9-Phenylfluorene	18.5[d]	152

[a] Notation: Biph, o,o'-biphenylene; DBBiph, 3,4,5,6-dibenzobiphenylene; Phen, 4,5-phenanthrylene.

[b] The standard acid for Compounds 3-7.

[c] The standard acid for Compounds 9-13, 15, 16, 18-29 and 32.

[d] The standard acid for Compounds 31, 33-38.

Polycyano CH-acids were studied in H_2SO_4/H_2O (1 to 70%) and $HClO_4/H_2O$ (1 to 70%) mixtures[25], or in $DMSO/Pr_3N$ ($1 \times 10^{-3}M$), DMSO/EtOH/EtONa, $DMSO/CH_3COOH/CH_3COONa$ ($1 \times 10^{-2}M$)[148,149],

The acidic hydrocarbons in Table 21 have extensive π -electron systems, so that the formation of carbanions should, first of all, affect the π electron energy. Wheland[153] assumed that the acidity should be proportional to the energy difference between a hydrocarbon and the conjugate anionic base, expressed as follows,

$$E_\pi(R^-) - E_\pi(RH) = 2\alpha + \Delta M\beta$$

$$pKa = a + b \cdot \Delta M$$

where ΔM is an HMO (Hückel molecular orbital) parameter, a and b are empirical constants.

The ΔM values calculated for many conjugated hydrocarbons are given in *refs* 146, 154-157. This equation does not include terms for σ-bond energies, solvation and spatial effects, and the incomplete overlap (non-planarity) effect.

Therefore, experimental points diverge significantly from the pKa vs. ΔM plot (Table 21). Bad correlations were also obtained by Streitwieser with the compounds of Table 6[3]. Consequently, CH-acidities cannot be very reliably predicted by the unextended HMO theory.

8. Other Methods

Recently Arnett et al[159] have proposed a thermochemical method for the direct measurement of the heat of deprotonation of CH-acids in DMSO. They measured the partial molar heat of dissolution, ΔHs of an acid in a very dilute solution (10^{-2}-10^{-3}M) of DMSO, (ΔHsDMSO) and then in a 0.1 M alkali dimsyl solution in DMSO (ΔHs dimsyl).

The heat of deprotonation (ΔH_D,) was found as follows.

$$\Delta H_D = \Delta H_S(\text{dimsyl}) - \Delta H_S\ (\text{DMSO})$$

The ΔH_D (kcal/mole) values obtained for 9-phenylfluorene (-24.1), 4,5-methylenephenanthrene (-18.3), fluorene (-18.2), triphenylmethane (-9.4), and tert-butanol (-9.2) correlate linearly with the pKa's of these acids in DMSO (Table 12) : $\Delta H_D = 1.35\ pKa - 47.4$

Jones et al.[160] determined acidities in DMSO by a kinetic method. They measured detritiation rates for a "standard" CH-acid in a number of DMSO/H_2O mixtures containing an exact amount of a base (0.010 M KOH). The procedure was repeated in the presence of the second acid, that was markedly ionised under these conditions and therefore dimished the OH^- concentration (and the H_- value) considerably. The decrease in the OH^- concentration decelerates the standard CH-acid detritiation rate. The hydroxyl concentration in the presence of the second acid, provided that the second anion does not catalise detritiation, may be written as follows,

$$[OH^-]_2 = [OH^-]_1 \cdot \frac{k_2}{k_1}$$

where $[OH^-]_1$ and $[OH^-]_2$ are the hydroxyl concentrations in the absence and in the presence of the second acid and k_1 and k_2 are the pseudo-first order rate constants of detritiation in the absence and in the presence of the second acid, respectively.

The concentrations of the second acid and its anion are

$$[R_2H] = [R_2H]_{initial} - [R_2^-]$$

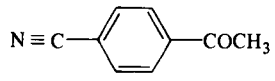
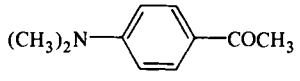
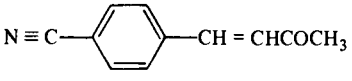
and

$$[R_2^-] = [OH^-]_1 - [OH^-]_2$$

whence, by using the relationship

$$H_- = pKa\ [R_2H] - \log\frac{[R_2^-]}{[R_2H]}$$

it is possible to obtain the value of pKa(R_2H) referred to a standard aqueous solution. This method was used by Jones[160] to study acidities of the following compounds.

	pKa (DMSO-H_2O)
Fluorene	21.0
	18.4
	22.6
$PhCH = CHCOCH_3$	21.4
	20.6

To estimate pKa's of CH-acids Caillet and Bauer[161] used the following equilibrium in dimethoxyethane,

$$R - Mg + R'-H \rightleftharpoons R'-Mg + R-H$$

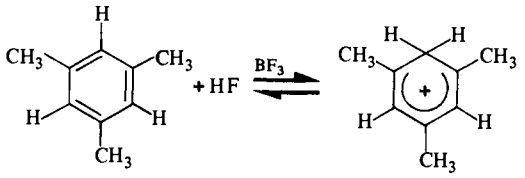
Its position was measured by potentiometry with the hydrogen electrode. Reasonable pka values were obtained as follows,

CH-acid :	Indene	PhC≡CH	Ph_3CH	Ph_2CH_2
pKa (DME):	$19\pm\bar{1}$	$23\pm\bar{1}$	$28\pm\bar{1}$	$34\pm\bar{1}$

but the value obtained for benzene (24) was too low.

9. Acidity of Arenonium Ions

Up to now the discussion has been limited to non-charged CH-acids, the type which embrace almost all organic compounds. Arenonium ions are a type of positively charged CH-acids, formed by the action of strong acids on arenes, e.g.



The CH_2 group adjacent to the conjugated system in these compounds is extremely acidic, e.g. benzenonium ion acidity in water is much higher than the acidity of the strongest non-charged acid which has been studied, viz, pentacyancyclopentadiene (pKa about -10, which is close to the value for the conjugate acid of the least basic dipolar aprotic solvent, acetonitrile $CH_3C{\equiv}\overset{+}{N}H$).

Arenonium ions have been observed by nuclear magnetic resonance, infrared and ultraviolet spectroscopic techniques. A comprehensive survey of the spectra and formation constants was made by Perkampus[162] whose results are discussed below.

Kresge et al.[163 165] found pKa values for arenonium ions in aqueous perchloric acid and aqueous sulphuric acid. The acidity function H_0 does not work in concentrated (60% or higher) perchloric acid solutions, so a different function (H_C) was introduced which increases with concentration steeper than does (H_0). The pKa values found spectrophotometrically using H_C are listed in Table 22.

The application of nuclear magnetic resonance spectroscopy to the cationic acids listed in Table 22 showed unambiguously that the methylene protons in these compounds had an aliphatic character.

Other arenonium acidities were measured in anhydrous hydrofluoric acid (Table 23). These pKa values are valid only in hydrofluoric acid but the relative pKa values obtained in this solvent would apply to other solvents[162]

The data of Tables 22 and 23 demonstrate that the introduction of electron releasing substituents in the ring, and an increase in the number of condensed rings, diminish the arenonium acidities, in other words, the aromatic hydrocarbons become stronger bases.

TABLE 22

Acidities of Arenonium Ions in Perchloric Acid at 25°C[165]

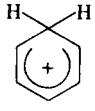
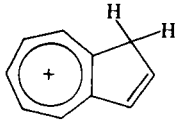
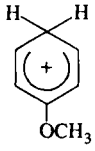
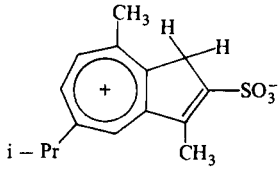
Acid	pKa	Acid	pKa
	− 23.0		− 1.7 /ref. 166/
	− 15.3		− 0.6 /ref. 167/

Table 22 *continued*

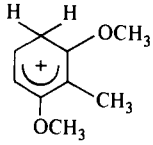
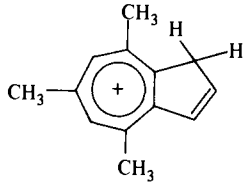
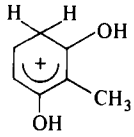
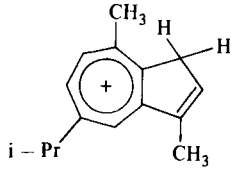
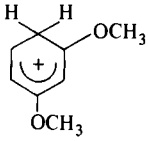
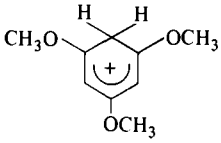
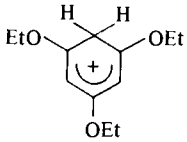
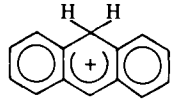
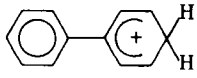
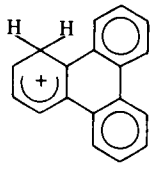
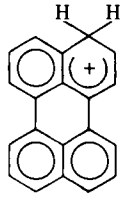
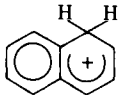
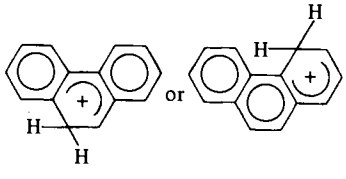
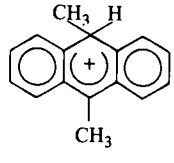
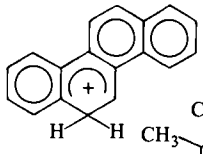
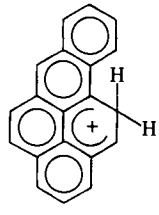
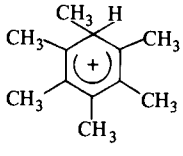
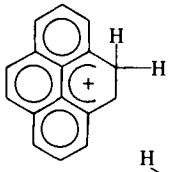
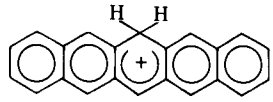
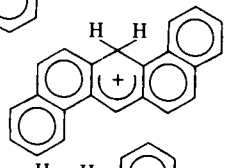
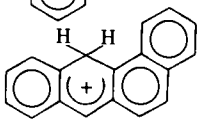
Acid	pKa	Acid	pKa
	-9.3		+ 0.5 / ref. 167/
	-7.5		+ 1.5 /ref. 167/
	-9.0		
	-5.7		
	-4.8		

TABLE 23

Acidities of Arenonium Ions in Anhydrous Hydrofluoric Acid at 0°C[162 168]

Acid	pKa	Acid	pKa
	− 9.2		3.8
	− 5.5		
	− 4.6		4.4
	− 4.0		
	− 3.5		6.4
	− 1.7		6.5
	0.4		
	2.1		7.6
	2.2		
	2.3		

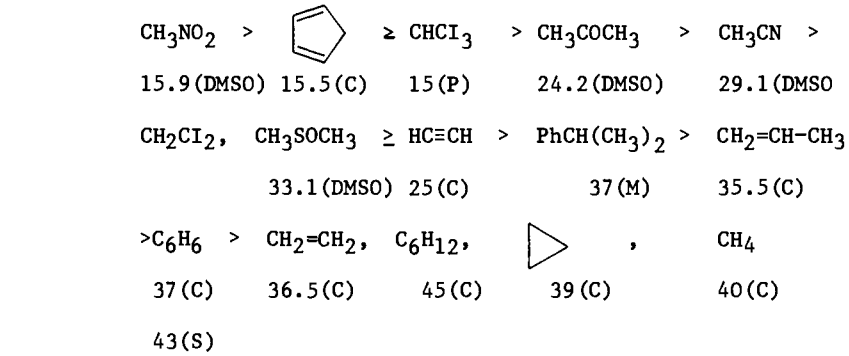
Chapter II

Structure Effects on Equilibrium CH-Acidity

I. Acidity in the Gas Phase

Cram[2] extensively discussed CH-acids from the point of view of effects on pKa and carbanion stabilisation mechanisms. Here attention will be focused in a general way on the principal structural effects. These are induction, conjugation (including aromatisation, hyperconjugation, homoconjugation), α-effect, and *d*-orbital effects leading to the so-called gauche-effect.

To begin with, the empirical pKa values are complicated functions of solvent effect and intramolecular polar and spatial interactions. To estimate inherent CH-acidity as a function of the structure, the solvent should be eliminated. It is, therefore, instructive to start with a study of acidity in the gas phase. Unfortunately these types of data are extremely scarce[12,61]. CH-Acidity in the gas phase decreases across the following series.*



Generally speaking, hydrocarbon acidities in solvents such as dimethylsulphoxide (DMSO), dimethylformamide(DHF), cyclohexylamine, benzene, ether are a reflection of the acidities in the gas phase; only acetylene, which is a weaker acid in the gas phase than is dimethylsulphoxide or methylene chloride does not follow this relationship.

Brauman and Blair[12] noted that although butylacetylene (BuC≡CH) and methylacetylene (MeC≡CH) are weaker acids than is unsubstituted acetylene (CH≡CH) (in accord with +I effect of alkyl groups) butylacetylene is a stronger acid than is methylacetylene. They found that in the gas phase there is a trend for longer alkyl groups to lead to a better anion charge stabilisation in

*The pKa values are given under the formulae. They key to the letters in parenthesis is as follows: DMSO, in dimethylsulphoxide: C, Cram MSAD: P, polarographic: M. McEven: S Streitwieser.

acetylenes. The same was found for alcohols:[107]

$(CH_3)_3CCH_2OH > (CH_3)_3COH > (CH_3)_2CHOH > CH_3CH_2OH > CH_3OH > H_2O$;
$(CH_3)_3COH \sim n\text{-}C_5H_{11}OH \sim n\text{-}C_4H_9OH > n\text{-}C_3H_7OH > CH_3CH_2OH$

This is explained in terms of an electrostatical model of charge interaction with a polarisable alkyl group (cf. Chapter I). Recently the first quantitative data have been reported by Mahon et al[93] on CH-acidity in the gas phase. The "intrinsic" acidity was shown by these workers to decrease in the following order (in parenthesis the values of RH bond energy minus electron affinity of R·radical are given in kcal/mole):

dicyanomethane (17.2) > acetylacetone (28) > phenylacetonitrile (35) > acetophenone (45.6) > diphenylmethane (47.0) > propylene (66.9) ~ toluene (66.9) > methane (~100).

II. Acidity in Solution

Any generalisations based on a quantative treatment of acid-base systems in solution are of great practical significance, since organic reactions are usually carried out in solution. The effect of the structure on the pKa in the condensed phase is discussed below. The data discussed below has been obtained over the past ten years.

1. Hydrocarbons. s-Character. Conjugation

Cram[2] and, later, Maksic et al[88,123] have shown that hydrocarbon acidities correlate linearly with the s-character of the orbital carrying the carbanion negative charge. The higher the s-character the more stable is the carbanion. That is why acidity increases in the series methane < cyclopropane < ethylene ~ benzene < acetylene. On the other hand, the CH bond s-character governs also the coupling $^{gem}J(^{13}C\text{-}H)$ in the PMR spectra of the CH-acids.[168] Consequently, a linear relationship of pKa with $J(^{13}C\text{-}H)$ may be expected, bound to certain limitations (see below). The plot is shown in Fig. 8.

The straight line in Fig. 8 is drawn through the points corresponding to HCN, $PhC{\equiv}CH$, $HC{\equiv}CH$, CF_3H, C_6H_6, cyclo-C_3H_6, CH_4. In the respective carbanions the charge is localised, in other words, hybridisation of the carbon orbital of the carbon-hydrogen bond in the non-ionised state does not essentially differ from hybridisation of the negatively charged orbital in the carbanion. When there is no rehybridisation the inductive effect proper is felt.

When the hydrogens in methane are replaced by (-M)-groups the constant J increases across the following series: $CH_3SO < CH_3CO < CN < NO_2$. This corresponds to an increase in the inductive (-I) effect of the substituents [173].

If the points corresponding to these compounds had not diverged from the straight line, the plot in Fig. 8 could have given the following induction-induced acidity increments: CH_3SO, 1; CH_3CO, 2-3; CN, 4-5; and NO_2, 6-7 pKa units. Thus, if the carbon orbital s-character had been invariable, the nitromethane acidity would have been between that of methane and benzene.

However, the presence of (-M)-substituents causes deviations towards lower

pKa values, increasing in the series: CH_3SO < CN < CH_3CO < divinylene < NO_2. This corresponds to a conjugation effect series of these substituents. The deviation found permits one to qualitatively estimate rehybridisation occurring on going from a CH-acid to the anion. This is at its highest (ca. 35 pKa units) with nitroalkanes where the charge in the anion is almost totally localised on the oxygen.

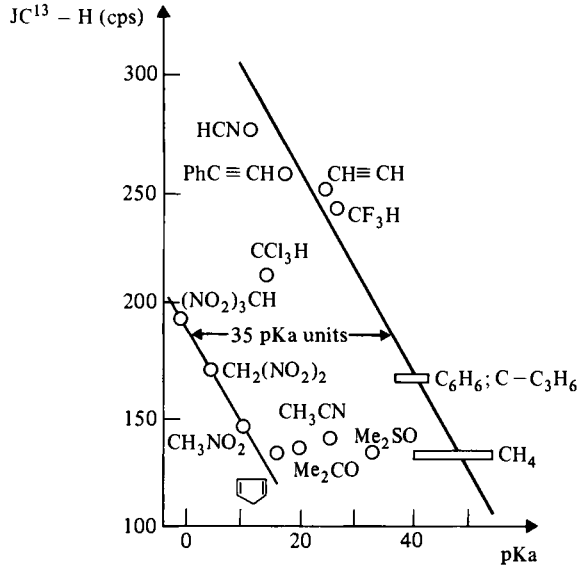


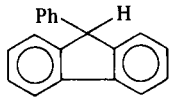
Fig. 8. Comparison of inductive and resonance contributions in carbanion stabilisation, from spectral date. (The $J(^{13}C\text{-}H)$ values are from Ref. 168).

This data illustrates the tremendous role played by conjugation in the stabilisation of carbanions. In the case of the cyclopentadienyl anion, conjugation leads to the aromatic structure. If no conjugation had occured, cyclopentadiene would have been only 1-2 pKa units more acidic than methane. Its experimental acidity (pKa 15.5 Cram) is due exclusively to aromatisational stabilisation of the anion.

Hydrocarbon acidities lie in a very wide range[174]. Hydrocarbons are known whose acidities are comparable with acidities of mineral or carboxylic acids, or phenols, in water. The respective carbanions are, as a rule, strongly conjugated systems, often aromatic (e.g. cyclopentadiene). Other examples occur, the Kuhn hydrocarbons[148, 175-177] as illustrated overleaf.

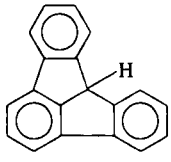
The data given demonstrates that hydrocarbons whose carbanion negative charge is delocalisable over the cyclopentadienyl carbons are particularly acidic. This is related to the aromatisation effect predicted by the molecular orbital theory. The cyclopentadienyl anion is isoelectronic with benzene, the indene anion with napthalene, the fluorene anion with phenanthrene. That

Scheme A
Kuhn's Hydrocarbons



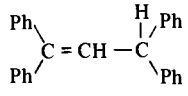
9-Phenylfluorene

pKa 18.5 (S)



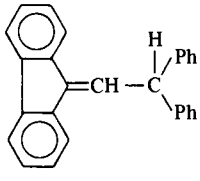
Fluoradene

pKa 11 (H_2O),
13.5 (MeOH),
13.8 (DMSO,
ref. 178)



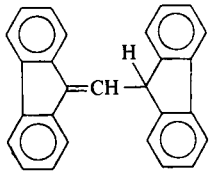
1,1,3,3-Tetraphenyl-propene

pKa ca. 15 (H_2O)



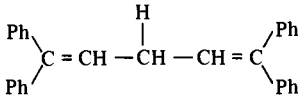
1,1-Biphenylene-2,3-diphenylpropene

pKa ca. 15 (H_2O)



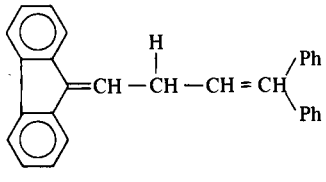
1,1,3,3-bis(Bipnenylene)propene

pKa ca. 10 (H_2O), 13.8 (S)



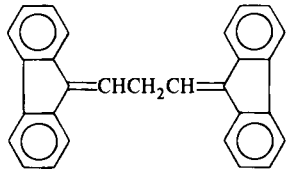
1,1,5,5-Tetraphenyl-pentadiene-4

pKa ca. 15 (H_2O)

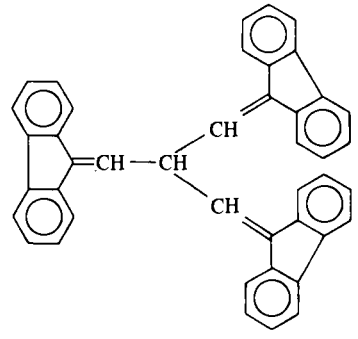


1,1-Diphenyl-5,5-diphenylene-pentadiene-1,4

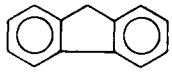
pKa ca. 10 (H_2O)



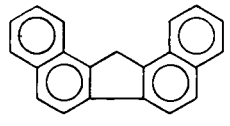
1,1,5,5-(Biphenylene)pentadiene-1,4
pKa 8.8 (H_2O)



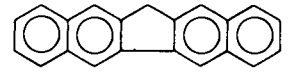
tris-(Biphenylene-vinyl)methane
pKa 6.2 (H_2O)



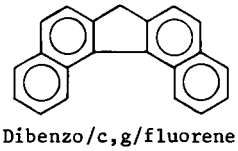
Fluorene
pKa 20.5 (ref. 148)
in EtOH-DMSO-EtONa)



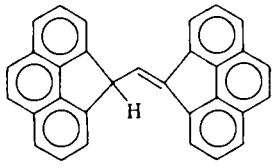
Dibenzo/a,f/fluorene
pKa 17.5 (ref. 148)
in DMSO-EtOH-EtONa)



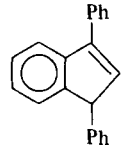
Dibenzo/b,h/-fluorene
pKa 21.4 (ref. 148)
in DMSO-EtoH-EtONa)



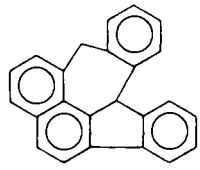
Dibenzo/c,g/fluorene
pKa 16.8 (ref. 148,
in DMSO-EtOH-EtONa)



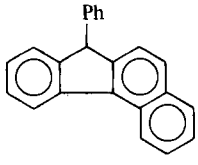
1,1,3,3-bis(Phenanthrylene) propene
pKa 13.26 (M, ref. 178)



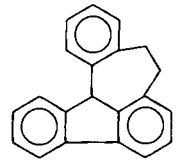
1,3-Diphenylindene
pKa 13.22 (S, ref. 178)



1,12-(o-Phenylene)-7,12-dihydropleyadene
pKa 15.36 (S, ref. 178, 179)



9-Phenylbenzo/c/fluorene
pKa 15.67 (S, ref. 178)



Bishomofluoraden
pKa 17.36 (S, ref. 178)

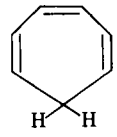
(S) Streitwieser
(M) McEaven

DMSO dimethylsulphoxide

is why the anions have higher stabilities.

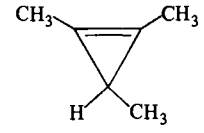
In contrast, the anion of cyclopropene is extremely unstable, owing to its "antiaromaticity". Cycloheptatriene, whose anion is neither aromatic nor *anti*aromatic, is almost as acidic as is propylene.

pKa 15.5 (C)



pKa 36 (B)

(B, Breslow scale)



pKa 62 (B)

(C, Cram scale)

The acidity of polyarymethanes as a function of structure was studied comprehensively by Steitwieser et al[174]. They identified the three factors playing the most important role as being, (a) the number of phenyls bonded with the acidity centre (triphenylmethane > diphenylmethane > toluene > methane), (b) coplanarity of the phenyls bonded with the acidity centre (xanthene > diphenylmethane; 9-phenylxanthene > triphenylmethane), and (c) the presence of a five-membered ring (fluorene > diphenylmethane, 1,1,5,5,-bis(biphenylene)pentadiene-1,4 > 1,1-diphenyl 5,5-diphenylenepentadiene-1,4 1,1,5,5-tetraphenylpentadiene-1,4). The acidities of compounds whose anions are planar (indene, fluorene, toluene) correspond to those calculated via the molecular orbital theory. In the case of the non-planar anions, this correlation does not hold and the expected deviations towards lower acidity occur[89,179].

An increase in electron withdrawal resulting from inductive and conjugation effects caused by replacing a phenyl group by hydrogen causes an appreciable increase in carbanion stability. p-Biphenylyldiphenylmethane is 1.3 pKa units more strongly acid than is triphenylmethane. The replacement at the acidity centre leads to greater effects on acidity, e.g. triphenylmethane is 1.6 pKa units more acidic than is diphenylmethane, and 9-phenylfluorene is 5.3 pKa units more acidic than fluorene. In all these cases, however, the phenyl substituent does not lie on the conjugation plane, so the acidity increase observed is not due to maximal overlap of the π-orbitals. It will be recalled that 9,9-dimethyl-10-phenyldihydroanthracene, a triphenylmethane analogue in which coplanarity of the benzene rings exceeds that in triphenylmethane , has a pKa which is 3.5 units lower than that of triphenylmethane (despite the presence of an electron donor alkyl bridge). The phenyl groups in triphenylmethyl anion deviate by 30-40° from the conjugation plane[276]. On the other hand, 9-phenylfluorene differs from triphenylmethane by 13 pKa units. Consequently, it may be assumed that the increment due to the coplanarity is of about 4 pKa units while the increment due to the cyclopentadienyl ring is 9 pKa units[174].

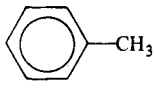
Accordingly, structural factors stabilising polyarylmethyl anions may be arranged in the following series of their efficiency: cyclopentadienyl ring >> coplanarity of benzene rings >> inductive effect of C_6H_5 groups.

Acidities of polyarylmethanes increase steeply with the introduction of electronegative substituents. The p-nitrophenyl group acts almost identically to the perfluorophenyl group.

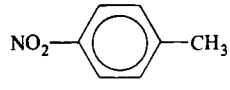
$(C_6F_5)_3CH$ pKa 15.8 (Ref 175)

$(4\text{-}NO_2C_6H_4)_3CH$ pKa 17.4 (ref. 48); 12.2 (DMSO)

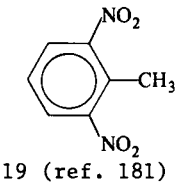
The examples shown above demonstrate how important is conjugation in the case of the p-nitrophenyl group. The effect is as strong in the benzyl anion.



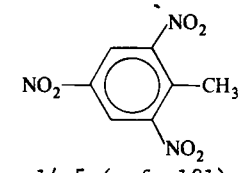
pHa : 35 (C)
(C = Cram)



26 (ref. 180)



19 (ref. 181)



14.5 (ref. 181)

The role of conjugation may be easily illustrated by collating acidities of the saturated and unsaturated olefinic compounds which do or do not contain carbonyl groups (Table 24.)

TABLE 24

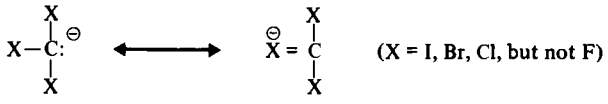
Effect of Carboalkoxy Group on Acidity of Aliphatic and Olefine Compounds[182]

Compound	pKa	ΔpKa	Compound	pKa	ΔpKa
CH_4	57(P)	16 to 33	$CH_2=CH_2$	36(C)	4
	40(C)				
CH_3COOR	24(P)		$CH_3CH=CHCOOR$	32(P)	

(C) Cram scale, (P) polarographic scale.

The data of Table 24 suggest that the carboalkoxy group has only a small effect on the olefine α-proton acidity. Indeed, the pKa difference between ethylene and methyl crotonate is only 4 pKa units whereas it is much higher (>16 units) between methane and ethyl acetate. Consequently, the carbonyl-induced stabilisation of a carbanion is effective only if the charge is built up on the saturated carbon, because it is only in this case that the (-M) effect may play its role to the fullest extent.

For an unsaturated molecule, such a stabilisation is less probable because the allenic structure (I) is unfavourable.



(X = I, Br, Cl, but not F)

Partial delocalisation of the charge in this case may be due merely to the carbonyl (-I) effect.

2. Compounds Containing Fluorine or Other Halogens. α-Effect

Fluorine α-positioned vis-a-vis a carbanion centre may raise as well as lower the acidity. Generally speaking, the fluorine effect on acidity is not predictable.

The situation is more predictable in the case of other halogens. Thus the introduction of chlorine into a saturated hydrocarbon molecule raises the geminal C-H bond acidity. The second and the third chlorines raise the acidity even higher, so the chloroform proton is eliminated even under the action of a concentrated potassium hydroxide solution in water.

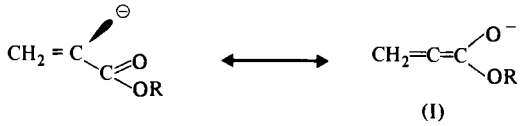
The chlorine effect is due to negative inductive effect. The latter increases from iodine to fluorine, so haloform acidities might be expected to rise across the following series:

$$CHI_3 < CHBr_3 < CHCl_3 < CHF_3$$

Experimentally, however, the reverse order is found:

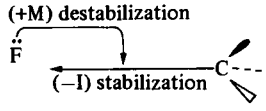
	CF_3H	<<	CCl_3H	<	CBr_3H	~	CI_3H
pKa(P):	26,5		15		9		-
pKa (ref.140):	28(ref.2)		15.5		13.7		13.7

It is seen that fluoroform is the weakest acid among the four haloforms. Consequently, alongside with their inductive effect, halogens should exert another effect, either (i) an additional stabilisation increasing from fluorine to iodine or (ii) a destabilisation increasing from iodine to fluorene. The effect (i) was assigned to participation of the d-orbitals in charge stabilisation[183]. Theory[183] states that the lowest acidity of fluoroform is due to the impossibility of resonance in which the d-orbitals would participate (zero contribution of the structures containing ten electrons in the external shell).



(I)

A more probable assumption is that a destabilisation of the (+M) type has a role[140,184].



This effect, known as anticonjugation, is at its strongest for fluorine, which lies in the same period as carbon. The unfavourable repulsion of electrons that occupy filled orbitals carrying the anion negative charge and the fluorine lone pair is in this case maximal. Consequently, the introduction of fluorine into the molecule may have no effect on or even diminish the acidity[185].

The α-effect is probably at its weakest when the angle between the filled fluorine orbital and the negatively charged carbon orbital is 90° and at its strongest when the carbanion is flat. Thus, the α-effect should hinder the formation of planar configuration and should be looked for, in the first place, among carbanions in which there is conjugation with (-M)substituents.

The polarographic acidity of substituted acetic esters increases in the following order;

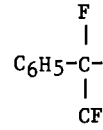
	$CF_2HCOOEt$ (polarographic)	CH_3COOMe	$CH_2FCOOEt$	$CFClCOOEt$
pKa:	25	24	21	18

The acidity of ethyl trifluoroacetate is about 3 pKa units higher than that of methyl acetate. However, ethyl difluoroacetate has, if anything an acidity which is a little weaker than that of the unsubstituted acetic ester. Consequently the introduction of one fluorine raises, whereas the two fluorines lower, the acidity. These results agree with the data obtained by Hine[185] on hydrogen isotope exchange rates in the compounds under discussion. In methanol at 35°C, methyl fluoroacetate exchanges its hydrogen for deuterium twice as fast as does ethyl acetate, whereas methyl difluroacetate exchanges its hydrogen for deuterium 5,000 times slower, than does ethyl acetate. The destabilising effect of chlorine, if at all present, is markedly weaker than that of fluorine.

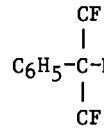
The fact that there is no correlation of the acidities of fluoro hydrocarbons with the fluorine inductive effect is clearly demonstrated by the following series of increasing acidity in which it is seen that the introduction of fluorine into bis(trifluoromethyl)methane$(CF_3)_2CH_2$ to produce $(CF_3)_2CHF$ is almost without effect on acidity whereas the inductive effect of introducing another (CF_3) group to produce $(CF_3)_3CH$ has a tremendous effect on acidity[181].

	$(CF_3)_2CH_2$	$\sim$	$(CF_3)_2CFH$	$\ll$	$(CF_3)_3CH$
pKa (polarographic)	22		22		7
pKa (literature)			18.0[140]		11[141]

The same effect is seen below on comparing the acidities obtained in methanol for the fluorinated benzyl hydrocarbons[186].



pKa ca.30



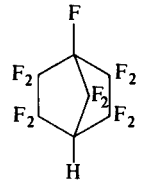
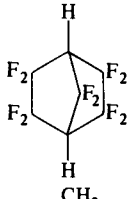
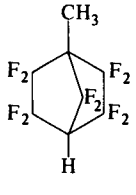
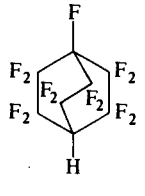
pKa ca.25

The overwhelming acidifying effect of CF_3 against F (often ascribed to negative hyperconjugation[141] of CF_3: see, however ref.187) follows also from the fact that CH_3COOCH_3 differs in acidity from $CH_2(CF_3)COOC_2H_5$ by 8 pKa units whereas the difference between CH_3COOCH_3 and $CH_2FCOOC_2H_5$ is only 3 pKa units (polarographic scale).

Streitwieser and Holtz[187,188] studied hydrogen isotope exchange in polyfluorinated bicycles of the norbornane and bicyclo/2.2.2/-octane types. Table 25 lists the pKa values, estimated from the hydrogen for tritium exchange rate constants measured in methanol in the presence of sodium methoxide[181]. An arbitrary reference compound in Table 25 is fluoroform whose pKa is taken as 26.

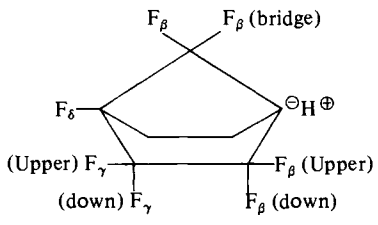
TABLE 25

Acidities of Perfluoro Hydrocarbons in Methanol[188]

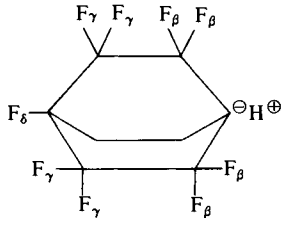
No.	Acid	pKa	No.	Acid	pKa
1.	$C_6H_5CF_2H$	30	6.	$(CF_3)_2CFH$	20
2.	CF_3H	26(P)			
3.	$CF_3(CF_2)_5CF_2H$	25	7.		17
4.		21	8.	$(CF_3)_3CH$	15
5.		21	9.		13

(P) polarographic scale

To find the effect of fluorine on CH-acidities, Streitwieser and Holtz[187 188] introduced a simple electrostatic model of the field effect. Each of the C-F bonds was simulated by a unit dipole lying in parallel with the bond, and the electrostatic potential was calculated from the interaction of the dipoles with the ionised C-H bond at the bridgehead of the bicyclic system. It was compared with the potential of $(CF_3)_3C^-H^+$. There are six C-F bond types in the norbornane, only three in the bicyclo 2.2.2 octane.



Norbornane

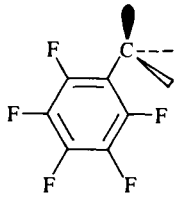


bicyclo 2.2.2 octane

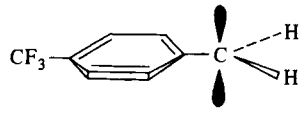
The total electrostatic energy may be correlated with the energy of interaction of the equivalent number of β-fluorines in $(CF_3)_3CH$ or, in equivalent terms with the Taft σ* parameters. Streitwieser and Holtz[187 188] showed that the correlation is linear. The Taft values for the α- and β-fluorines are σ* (α-F)=1.71 and σ* (β-F)=0.95. If the correlation is extrapolated to lower acidities, the point of the α,α-difluorobenzyl anion will lie on the point of toluene outside the straight line. The correlation includes only the inductive effect of fluorine, therefore the divergence of toluene suggests that the α,α-difluorobenzyl anion is a pyramid whereas the benzyl anion is planar.

The ratio of the Taft δ* constant for a substituent α-positioned vis-a-vis the reaction spearhead to the constant for the β-substituent is known to lie at 2.5 to 3.0 with an average value of 2.7[173]. However, for fluorine the ratio δ* (α-F)/ δ* (β-F) is 1.8 i.e. markedly lower. This may be explained by assuming that an overlap of the carbanion lone pair with the fluorine lone pair destabilises the carbanion significantly. The overlap leads to pyramid structures for fluorinated anions such as CF_3.

A comparison of the pKa values of $C_6F_5CH_3$ and p-$CF_3C_6H_4CH_3$ (25 and 28 both in polarographic scale) shows that the effect of pentafluorophenyl group is slightly stronger than is that of the p-CF_3group. This may be due to a difference between the (I) and (II) structures illustrated below, in which the anion (II) is planar whereas (I) is a pyramid. It is possible that the fluorine (+M) effect might destabilise the planar perfluorophenylmethyl anion.



I



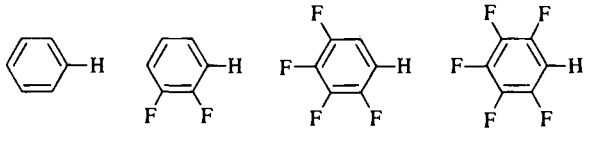
II

The planarity of (II) may be due to negative hyperconjugation of the anion centre with the CF_3 group.*

Table 26 contains the data which show the halide substituents effects on equilibrium acidity of polyfluorinated hydrocarbons[140]. The introduction of chlorine, bromine or iodine results as for the haloforms, in an increasing acidity, but the effect of the introduction of fluorine is either weak or actually decreases the acidity.

A conclusion is that the ability of halogens to stabilise negative carbanion charge, i.e. F << Cl < Br ~ I, does not correspond to the order of their inductive effects. Methoxy groups may exert an even stronger destabilisation α^- effect than does fluorine (Table 26)

In fluorinated benzenes, an increased CH-acidity is due to the electron-acceptor properties of fluorine[190]. The Streitwieser acidity of benzene varies with the extent of fluorination as follows[191].



pKa: (Streitwieser scale) 43 34.98 31.52 25.85

*Although the existence of negative hyperconjugation has been queried[187 189], there are, nevertheless, instances such as this where it does explain phenomina which would otherwise be difficult to explain. The query[187 189] is due, inter alia, to the fact that the dipole moment increment in p-substituted dimethylanilines, due admittedly to hyperconjugation, is almost identical for p-CF_3 and p-$CF(CF_3)_2$. The conclusion was that the C-F and C-CF_3 bonds underwent the same no-bond resonance. This seemed highly improbable since "the acidity of hydrogen fluoride is at least 30 powers of ten greater than that of HCF_3"[189]. The large difference, however, relates to pKa (HF) measured in water. It has been noted already (Chapter I) that hydrogen fluoride in dipolar aprotic solvents and in the gas phase is a rather weak acid comparable with methyl cyanide (pKa 29 in dimethylsulphoxide). Thus inherent stabilities of F^- and CF_3 do not differ much, so the C-CF_3 no-bond resonance is, from this point of view, as possible as it is for the C-F bond.

TABLE 26

Equilibrium Acidity of Substituted Polyfluoro Hydrocarbons in DMSO/MeOH 1/1[140].

Acid	pKa	Acid	pKa
1. Compounds of the $CF_3CH(X)CF_3$ type			
1. $CF_3CH(CF_3)CF_3$	11[177] 7(P)	5. $CF_3CH(C_6H_5)CF_3$	17.9
2. $CF_3CH(Br)CF_3$	11.5	6. $CF_3CH(F)CF_3$	18.0
3. $CF_3CH(CI)CF_3$	12.6	7. $CF_3CH(OCH_3)CF_3$	>22
4. $CF_3CH(I)CF_3$	13.7	8. $CF_3CH_2CF_3$	22(P)
2. Compounds of the CF_3CX_2H type			
9. CF_3CBr_2H	16.9	11. CF_3CCI_2H	17.2
10. CF_3CI_2H	17.1	12. CF_3CF_2H	27

P = polarographic DMSO = dimethylsulphoxide.

The ortho-fluorine effect is evidently the greatest. Pentachlorobenzene has a pKa of 31 (polarographic). Consequently, aryl anions in which the negatively charged orbital is in-plane with the benzene ring are stabilised par excellence by the fluorine inductive effect[190].

However, the para-fluorine group in toluene lowers the acidity of the α-C-H bond whereas the ortho- or meta-fluorine groups increase the kinetic acidity[192]. The strong acidifying influence of the ortho- and meta-fluorine groups is due to the (-I) effect whereas the ortho- and para-influences include (+M) effect as well. A superposition of the effects may explain the fact that the para-fluorine group stabilises the benzyl anion while the ortho-fluorine exerts a lower acceptor influence than does the meta-fluorine. This picture is similar to the fluorine effect pattern observed for the α-position in aliphatic systems.[190]

Acidities of polyfluorinated di- and triarylmethanes are listed on the Streitwieser scale in Table 8, Chapter I. The triphenylmethyl anion, whose α-carbon has an sp^2 hybridisation[193], is a good model for visualising inductive effects of the substituents because the benzene rings are arranged in a propeller-shaped configuration (the torsion angle is 31.7°[193], lowering their resonance interaction with the carbanion centre significantly. This is very important in polyfluorinated triphenylmethyl anions and makes them thermodynamically more stable than the non-fluorinated analogues. However, as can be seen in Table 8, the introduction of substituents such as methyl or methoxy in the para-position decreases the equilibrium acidities. Thus, a conjugation-induced donor effect cannot be ruled out.

Each of the C_6F_5 groups contributes about 5.2 pKa units to the $(C_6H_5)_3CH$

acidity. The ΔpKa values calculated for 9-phenyl- and 9-perfluorophenyl fluorenes[190 194] using the equation

$$pKa = -4.577\ \delta^* + 21.58$$

with a δ^* value of 1.9 for the C_6F_5 group[195] and a pKa of 18.6 for 9-phenylfluorene[194] gave a value of ΔpKa of 5.4, almost identical to the C_6F_5 contribution in the acidity of $(C_6F_5)_3CH$. The phenyl group in the 9-phenylfluorenyl anion deviates by 30–39° from the cyclopentadiene ring plane[174 196], therefore the calculation suggests that the C_6F_5 group stabilises the anion predominantly by its inductive effect.

Variability of the C_6F_5 resonance/inductive effects ratio was demonstrated on mesomeric carbanions of the type $(C_6F_5C^-RR')Na^+$, where R=R' is COOEt, CN, COPh, and others. The negative carbon is in the sp^2 state[190] which is favourable for the resonance interaction with the aryl group lying inplane with the mesomeric site of the anion. It was found that the R and R' contributions in charge delocalisation, and the sizes of the R and R' groups, govern the resonance and the inductive effects of the C_6F_5 group. The resonance effect lowers the acidity, the inductive effect raises it. The ΔpKa values for para-H and para-F CH-acids are listed below[190].

$p\text{-}HC_6F_4CH(COOEt)_2$	$p\text{-}HC_6F_4CH(CN)COOEt$	$p\text{-}HC_6F_4CH(CH)C_6F_5$	$p\text{-}HC_6F_4CH(CN)Ph$
$p\text{-}FC_6F_4CH(COOEt)_2$	$p\text{-}FC_6F_4CH(CN)COOEt$	$p\text{-}FC_6F_4CH(CN)C_6F_5$	$p\text{-}FC_6F_4CH(CN)Ph$
ΔpKa +0.5	+0.4	-0.1	0

In contrast, with derivatives of polyfluorophenylmalonic acid where the para-fluorine is an acceptor and in polyfluoroaryl acetonitriles the p-F for p-H replacement is either without effect on or diminishes ΔpKa, so para-F is now acting as a donor

TABLE 27

Acidities of Polyfluorinated Carbonyl Compounds and their Non-fluorinated Analogues, in Dimethoxyethane.

Compound	pKa	pKa per one C_6F_5 group	Ref. No.
$C_6H_5CH(COOEt)_2$	14.2	1.4	197
$C_6F_5CH(COOEt)_2$	12.8		197
$C_6H_5CH_2COC_6H_5$	16.1	0.8	200
$C_6F_5CH_2COC_6H_5$	15.3		198
$(C_6H_5)_2CHCOC_6H_5$	16.6	2.5	200
$(C_6F_5)_2CHCOC_6H_5$	11.5		199

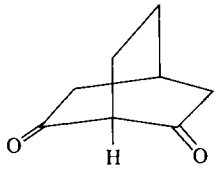
The data of Table 27 also suggest that the effect of C_6F_5 groups is dependent on the carbanion type. Thus, replacement of phenyl by C_6F_5 in desoxybenzoin $C_6H_5CH_2COPh$ does not lead to significant changes in the pKa value. An introduction of phenyl into desoxybenzoin slightly lowers the acidity of $Ph_2CHCOPh$, but decafluorobenzhydrylphenyl ketone is more acidic than pentafluorodesoxybenzoin (ΔpKa 3.8)

3. Compounds with Strongly Acidic Substituents Containing a Heteroatom. Conjugation.

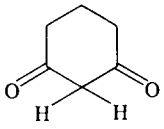
a. Aliphatic Nitro Compounds.

Carbanions in which the substituents can delocalise the charge with participation of atoms more electronegative than carbon should be more stable. That is why the acidic properties of nitro compounds, ketones, nitriles, etc. are all quite pronounced. Conjugation in a mesomeric anion makes the charge delocalise partially or predominantly on an electronegative heteroatom, and the carbanions should be planar (an sp^2-p configuration) or almost planar.

Indeed, the anions of tricyanomethane salts, pyridinium dicyanomethylide[201], and (β-carbamoylvinyl) dinitromethylide[202] are all found to be planar. The planar configuration may be distorted by steric or solvation factors. When the conjugation with the acidifying group is not possible (e.g. when the negative orbital cannot be complanar with the π -orbital of the group, then only the inductive effect operates and the acidity is markedly decreased. Examples of this kind have been discussed in the previous sections of this chapter. A further illustration of this may be found in the work of Bartlett and Woods[203], discussed below.



I



II

In the bicyclic β-diketone (I) the carbanion pair is localised on the sp^3 orbital and there is no conjugation with the π -orbitals of the carbonyls. The compound is, therefore, a very weak CH-acid. In the diketone (II), in contrast, conjugation is possible and this compound is a rather strong acid (pKa 5.26 in water)[36].

Pearson and Dillon[34] gave the following series of ability to acidify C-H bonds.

$$NO_2 > CO > SO_2 > COOH > COOR > CN \sim CONH_2$$

They noted that in water the effect was not additive with some of the substituents (Table 28) and explained this non-additivity by assuming that spatial repulsion makes some of the atoms in the anion deviate from complanarity. The effects are nearer to being additive in dimethylsulphoxide solvent (Table 28). This behaviour may be due to specific solvation. In aprotic dipolar solvents, anions are poorly solvated and the acidity is governed, to a first approximation, by structural effects on charge stabilisation. In protic solvents, additional stabilisation due to solvation of the negative spearheads by hydrogen bonds should operate. Delocalisation becomes stronger and naturally the hydrogen bond-induced solvation becomes weaker with an increase in the number of acidifying groups at the carbon of

the C-H bond under ionisation. The decrease in solvation may be compensated for by an increase in the number of hydrogen-bonded water molecules since the higher the number of acidifying groups the higher the number of electronegative atoms (O, N, and others) capable of hydrogen bonding.

TABLE 28

Successive Substitution Effect on CH-Bond Acidity in Water[34] and Dimethylsulphoxide (Table 12)

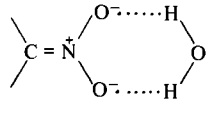
Compound	pKa in H_2O	pKa in DMSO
CH_3NO_2	11	15.1-16.6
$CH_2(NO_2)_2$	4	6.6
$CH(NO_2)_3$	0	below -1[204]
CH_3COCH_3	(20)	24.2
$CH_2(COCH_3)_2$	9	13.4
$CH(COCH_3)_3$	6	8.9[a)]
CH_3CN	(25)	29.1
$CH_2(CN)_2$	12	11.0
$CH(CN)_3$	(-5)[25]	(-7)[b)]

a) in dimethylformamide[239]
b) approximate estimates based on the reduction potential of $Hg(C(CN)_3)_2$ in dimethylformamide.

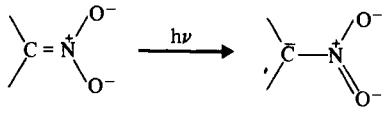
Consequently, pKa's measured in dimethylsulphoxide should be lower than those measured in water for compounds whose anions have their charge delocalised, this is because in dimethylsulphoxide the ability to form hydrogen bonds decreases and the affinity for dispersion interaction increases. On the other hand, dimethylsulphoxide should raise pKa's of compounds whose anions are conjugated. Probably, additivity of the substituent effects should not be studied in protic solvents.

Nitroalkanes both in the gas phase and in solution are among the strongest CH-acids. Their negative charge in the anions is significantly localised on the oxygen atoms, so these "carbanions" are, in fact, anions of the aci-forms.

The charge delocalisation on the oxygen atoms in the nitro group is dependent on the solvent. Hydroxyl-containing solvents solvate predominantly the oxygen site of the ambident anion by forming hydrogen bonds.



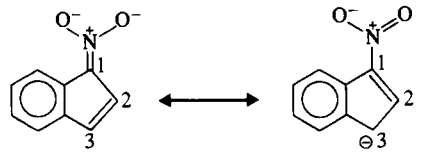
Thus hydroxyl-containing solvents favour delocalisation. Spectral data obtained for 1-nitroindene shows that the C_2-C_3 -bond order decreases by about



ground state excited state

10% on changing the solvent from deuterium oxide to hexamethylphosphorotriamidate[205].

The electron density distribution in nitroalkane anions may be pictured on the basis of their electronic spectra. These suggest that a $\pi \longrightarrow \pi^*$ transition occurs accompanied by a charge transfer from oxygen to carbon and a decrease in the C=N bond order[206-208].



Bathochromic shifts have been observed for nitroalkanes on changing the solvent from water to dimethylsulphoxide. This is interpreted as a measure of stabilisation of the ground state by hydrogen bonds[207]. The shifts, and the values of ΔpKa = pKa (in dimethylsulphoxide) - pKa (in water), are listed in Table 29. Parallelism between Δλ and ΔpKa is evident. Mononitro alkane anions are strongly solvated by protic solvents, whilst anions of di- and polynitro compounds are much less solvated by protic solvents. This agrees with electroconductivity data[209-213] showing that anions of these types have not acquired any significant solvent shells in either protic or dipolar aprotic solvents (Table 30).

TABLE 29

Bathochromic Shifts and Acidity Increments, obtained on Changing the Solvent from Water to Dimethylsulphoxide[207].

Anion	Δλ (nm)	ΔpKa pKa(DMSO) - pKa(H_2O)
$C(NO_2)_3^-$	0	-
$CH_3C(NO_2)_2^-$	0	1.4
$CH(COOEt)NO_2^-$	23	3.1
$CH(CH_3)NO_2^-$	38	7.7
$CH_2NO_2^-$	45	6.3

TABLE 30

The Number of Molecules in Solvent Shells of Anions of Nitrocompounds.

Anion	H_2O	DMF	CH_3NO_2	CH_3CN	CH_3COCH_3	MeOH	EtOH
$(NO_2)_3C^-$	0.9	0.1	0.3	0.3	0.3	1.1	0.4
$(NO_2)_2CH^-$	1.6	0.1	0.5	0.5	0.5	2.4	2.4
$(NO_2)_2CCH_3^-$	1.7	0.1	-	0.0	0.0	3.4	2.9

DMF dimethylformamide.

In hydroxyl-containing solvents, consequently, solvation of the nitroalkanes is a function of the number of nitro groups or the presence of other conjugable substituents in the molecule. That is why no unit correlation was found by Talvik[208] for acidity in a wide range of CH-acids of the type CHXYZ with no limitations imposed on X, Y, and Z. The effects of substituents on acidity is discussed below for various types of compounds.

Firstly the acidity of nitroalkanes is discussed in Table 31(Series 1) it is seen that for a range of substituted mononitromethanes the acidity increases in the following order:

$$CH_3NO_2 < CH_3CH_2NO_2 < (CH_3)_2CHNO_2$$

If only the methyl inductive effect had operated acidity should have decreased across this series. If it is assumed that the C-N bond order is close to two in the ground state of the anions, then the methyl group effect observed may be explained by hyperconjugation[228-232], or, alternatively, by an energy difference between the $C(sp^3)$-$C(sp^2)$ and $C(sp^3)$-$C(sp^3)$ bonds. If it is assumed that $C(sp^2)$-$C(sp^3)$ bond is ca. 0.04A shorter than the $C(sp^3)$-$C(sp^3)$bond[234], the $C(sp^2)$-H bond is ca. 0.02A shorter than (Csp^3)-H[233-235], while the relations $dE/_{dr}$ ~ 170 kcal/mole and $dE/_{dr}$ ~ 140 kcal/mole are valid for the C-C and C-H bond energies, respectively, then the ionisation energy difference expected on going from nitromethane to nitroethane is of about 4 kcal/mole. If, instead, the experimental hyperconjugation energies[233] are used, the nitroethane dissociation will be by about 2.3 kcal/mole more favourable than that of nitromethane.

The effect of halogens or CF_3 α-positioned to the ionisation site of nitroalkanes is mostly similar to the effect found in substituted esters (see Section II of this Chapter). Fluorine replaced by a hydrogen atom in nitromethane increases its acidity insignificantly (ΔpKa is 0.7). The effects of chlorine, bromine, and CF_3 are much higher (ΔpKa's are 3.0, 2.0 and 2.8 respectively). Introduction of a second fluorine atom makes the acidity of difluoronitromethane 2.2 pKa units lower than the acidity of nitromethane. Similarly, pKa $(NH_2COCH_2NO_2)$-pKa$(NH_2COCHFNO_2)$ is -0.7. However, dichloronitromethane is 4.2 pKa units more acidic than is the unsubstituted compound. The destabilising effect of fluorine in the planar anion of the aci-form may be due to anti-conjugation (α-effect transduced via the C=N double bond).

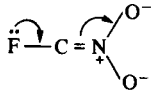


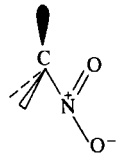
TABLE 31

Acidities of Nitro Compounds in Water at 25°C

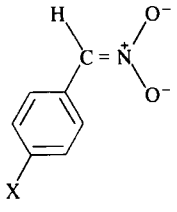
Compound	pKa	Ref. No.	Compound	pKa	Ref. No.
	1. Substituted mononitromethanes				
CH_3NO_2	10.21	22,43,214	$CH_3CH_2NO_2$	8.46	22, 43
CH_2FNO_2	9.5	215	$(CH_3)_2CHNO_2$	7.67	22
CH_2ClNO_2	7.20	216,217	$CHCl_2NO_2$	5.99	216
CH_2BrNO_2	8.20	217	$CHFClNO_2$	10.14	216
$CH_2(CF_3)NO_2$	7.40 (23°)	218	CHF_2NO_2	12.40 (20°)	218
$CH_3COCH_2NO_2$	5.10	34	$CHF(CF_3)NO_2$	9.11 (20°)	218
$NH_2COCH_2NO_2$	5.18	216	$NH_2COCHClNO_2$	3.60	218
$CH_2(CN)NO_2$	4.86 (27°)	219	$NH_2COCHFNO_2$	5.89	216
	2. Substituted dinitromethanes at 20°C				
$CH_2(NO_2)_2$	3.63	220,221	$NH_2COCH(NO_2)_2$	1.30	223
$CH_3CH(NO_2)_2$	5.30	220,221	$CH_3OOCCH(NO_2)_2$	0.98	223
$CHF(NO_2)_2$	7.70	221	$CH(NO_2)_3$	0.14	223
$CHCl(NO_2)_2$	3.53	222	$CH(CH)(NO_2)_2$	(-6.22)	223

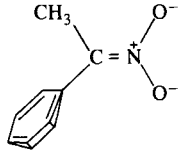
Compound	pKa	Ref. No.	Compound	pKa	Ref. No.
	2. Substituted dinitromethanes at 20°C *continued*				
$CHBr(NO_2)_2$	3.58	221,222	$CH(C_6H_5)(NO_2)_2$	3.89	224
$CHI(NO_2)_2$	3.19	221			
	3. Substituted alpha-nitrocarboxylic esters				
NO_2CH_2COOEt	5.82	34	$NO_2CHFCOOEt$	6.28	216
$NO_2CH(CH_3)COOEt$	6.57	225	$NO_2CHClCOOEt$	4.16	216
$NO_2CH(C_6H_5)COOEt$	6.9	226	$NO_2CH(CN)COOEt$	(-5.20)	222
	4. Vinylogues of substituted dinitromethanes				
$CH(NO_2)_2CH=CHCOOCH_3$	3.14	227	$CH(NO_2)_2CH=CHCOOCH_3$	1.93	227
$CH(NO_2)_2CH=CHSO_2CH_3$	1.65	227	$CH(NO_2)_2CH=CHNO_2$	0.07	227

This effect should favour a pyramid structure for the carbanion, hence distort the nitro/C^- conjugation and destablise the anion.

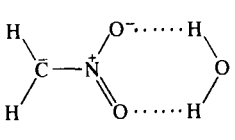


The two compounds $XC_6H_4CH_2(CH_3)NO_2$ and $XC_6H_4CH(CH_3NO_2$[231,236] differ from the nitro alkanes discussed above in that they obey good correlations of pKa with the Taft constants (σ or σ^*). A striking feature here is the apparent absence of any effect of conjugation with the para-X substituents in $RC_6H_4CH(CH_3)NO_2$[236]. It is noteworthy, however, that the phenyl effect proper is not felt either[208]. Thus the pKa of phenylnitromethane (6.88)[237] is 2 units lower than pKa of β-phenylnitroethane (8.78)[238] while ΔpKa for α-phenylnitroethane (pKa 8.52[236]) and 2-nitro-1-phenylpropane is as low as 0.6 units. Probably, the absence of conjugation is due to the non-coplanarity of the methyl-substituted compounds[258].

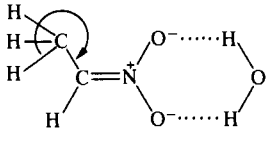




The introduction of methyl groups into dinitromethane or ethyl nitroacetate molecules (Table 31, Series 2 and 3) lowers their acidities, thus, the influence of hyperconjugation is not felt in these cases. This raises the difficult question as to why hyperconjugation is important in mononitro alkanes and yet does not play any significant role in dinitromethanes or ethylnitroacetates. Probably, as Fukuyama et al[231] have pointed out, the fact that mononitro alkanes solvate more effectively in water has a bearing on this situation.



worse solvation



better solvation

On the other hand, if it is assumed (see above) that dinitro and

nitrocarboalkoxyalkane anions are solvated by hydrogen bonds to a lesser extent than are mononitro alkane anions, owing to a greater charge delocalisation in the former species, then the weak effect of hyperconjugation will be explicable.

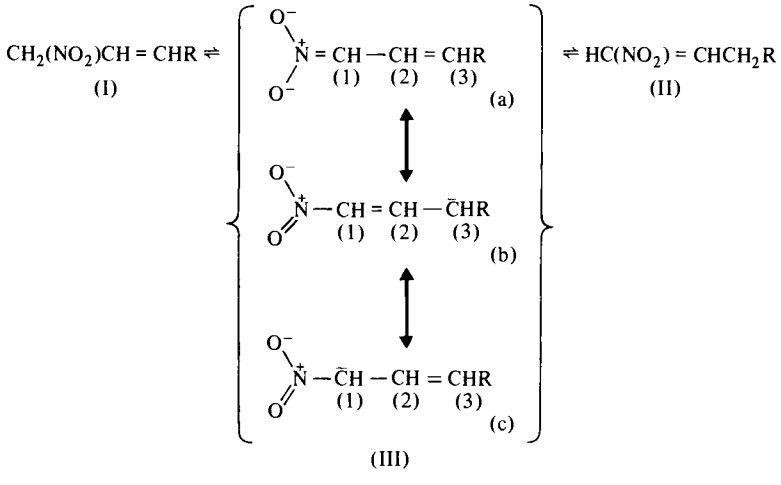
The effect of halogens on the acidities of dinitromethanes and nitroacetic esters is similar to the effect observed in other α-halo carbanions (see Section II of this Chapter), viz., the pKa decreases across the following series.

$$F > H > Cl \sim Br \sim I$$

The pKa values in 2-substituted vinyldinitro methanes (Table 31, Series 4) fit in well with an extended Hammett-Taft equation[227],

$$pKa = \sigma_I \rho_I + \sigma_R^- \rho_R + \text{const}$$

where the subscripts I and R reflect inductive and resonance substituent effects, respectively. The reaction constants are ρ_I -1.66 and ρ_R -7.95, that is, the pKa values are much more sensitive to the resonance effect than to the inductive effect. Proton magnetic resonance spectroscopy shows that in chloroform the tautomers (I) and (II) are equilibriated, in other words, the carbanion (III) can be protonated at two sites, C1 and C3.



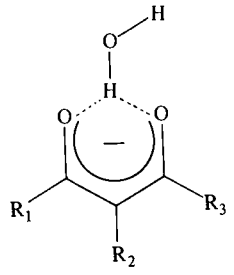
(III)

Consequently, the (IIIb) and (IIIc) contributions in the ground state of the carbanion are close and the anion (III) is planar.

b. β-Dicarbonyl and Other Compounds

In Table 32 are listed acidities of β-dicarbonyl compounds measured in water and in anhydrous dimethylformamide. No linear correlation exists between pKa's measured in these two solvents.

Data on the acidities of β-dicarbonyl compounds is insufficient to permit a detailed analysis of the structural effects. Spatial factors may be of primary importance as has been pointed out by Talvik[208]. β-Diketone anions in water probably have U-shaped conformations as shown below, where the groups R_1, R_2, R_3 can be subject to a spatial interaction and alter the strain in the structure (I).



(I)

TABLE 32

Acidities of Carbonyl Compounds in Water and Dimethylformamide at 25°C

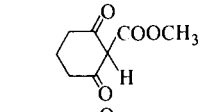
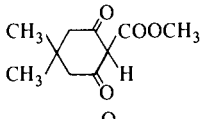
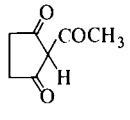
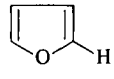
Compound	pKa in water	pKa in dimethylformamide[239]	Ref. No
1. β-Diketones			
$CH_3COCH_2COCH_3$	9.00	11.7	240
$CH_3COCH_2COCH_2CH_3$	9.32	-	241
$CH_3COCH_2COCH(CH_3)_2$	9.41	-	240
$CH_3COCH_2COC(CH_3)_3$	9.98	-	240
$CH_3COCH_2COC_6H_5$	8.73 (0.5% dioxan)	12.4	242
$C_6H_5COCH_2COC_6H_5$	9.08 (5% dioxan)	13.2	242
$CF_3COCH_2COCF_3$	5.3	-	274
$CH_3COCH_2COCF_3$	6.24	5.1	243
$C_6H_5COCH_2COCF_3$	6.79	8.1	274
	6.3		244
$CH_3COCHPhCOCH_3$	6.54	-	274
	9.28		245
$CH(COCH_3)_3$	5.86	8.9	246
$CH_2(CHO)_2$	5.00	-	35
		10.0	
		10.2	
		7.5	

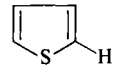
TABLE 32 *continued*

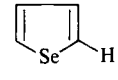
Compound	pKa in water	pKa in dimethylformamide[239]	Ref. No
2. β-ketoacid derivatives			
CH_3COCH_2COOEt	10.68	12.6	247
$CH_3COCH(C_2H_5)COOEt$	12.87	12.5	248
$CH_3CH_2COCH_2COOEt$	11.07	-	248
$(CH_3)_2CHCOCH_2COOEt$	-	12.9	-
$(CH_3)_3CCOCH_2COOEt$	-	14.1	-
$(CH_3)_2CHCOCH(C_2H_5)COOEt$	-	13.2	-
$CH_3COCHPhCOOEt$	10.43	-	248
$C_6H_5COCH_2COOEt$	-	12.9	-
$p\text{-}NO_2C_6H_4COCH_2COOEt$	-	11.3	-
FCH_2COCH_2COOEt	-	11.2	-
CF_3COCH_2COOEt	-	7.4	-
$C_6H_5CH_2COCH_2COOEt$	-	12.1	-
$EtOOCCH_2COCH_2COOEt$	-	11.3	-
$CH_3COCH(CN)COOEt$	-	6.0	-
$C_6H_5COCH(COOEt)COOEt$	-	10.2	-
$C_6H_5COCH_2CN$	7.77	-	249

4. Five-Membered Aromatic Heterocyclics. Inductive and Resonance Effects.d-Orbital Effect.

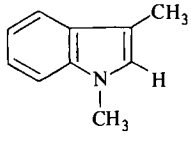
Five-membered heterocyclics have the following features in common: (i) anions with their charge localised in position 2 are more stable than are anions with the charge in position 3 and (ii) the acidity increases as the heteroatom goes down a Group of the Periodic System[250].

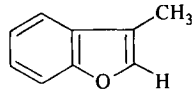


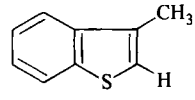


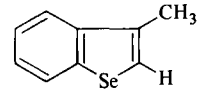


pKa: 36 (P) | > 35 (P) 38 (S) | < 35 (P)

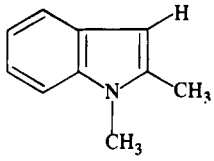


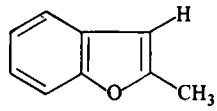


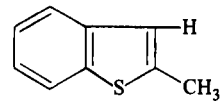


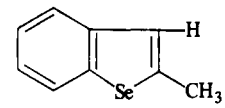


pKa: 36 (P) | > 35 (P) 37 (S) | 35 (P) 37 (S) | 34 (P)





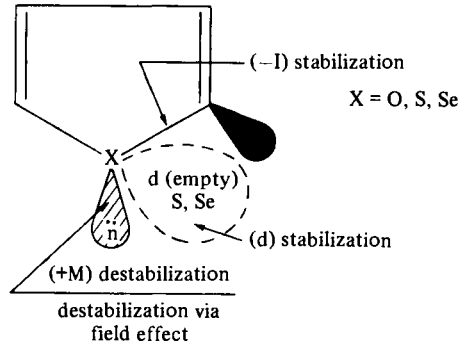




pKa: > 38(P) 37 (P) > 36 (P) < 36 (P)

(P) = acidity polarographic scale
(S) = acidity Streitwieser scale.

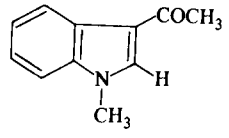
An increase in the anion stability observed on going from furan to selenophene may be explained by the simultaneous action of inductive, resonance, and d-orbital effects-



Barring all effects except inductive (-I), the stability should have risen in going from selenophene to furan derivatives, in perfect contrast with the experimental results. In view of the preceding results (Section 2 of this Chapter), it may be assumed that heteroatom lone pairs destabilise the carbanion centres. The effect is felt only in planar carbanions where the negative charge is localised on the sp^2 hybrid orbital. An increase in the heteroatom radius lowers the overlap of the lone pair with the orbital bearing the negative charge, so the unfavourable effect decreases. On the other hand, the increased stability of carbanions of thiophene and selenophene may be assigned to participation of the S and Se d-orbitals.

The lower acidity of the 3-hydrogen in compounds with the same heteroatom may be explained by assuming that the heteroatom (-I) effect falls down as transduced along the C-C bonds chain. It is still nor clear, however, why the acidity in the position 3 also rises with heavier heteroatoms, since the d-orbital and (+M) effects should not have affected the negative center in the position 3.

It is possible that the direct field effect, i.e. an interaction of the orbital bearing the negative charge of the carbanion with the lone electron pair of heteroatom, is the main effect on position 2. . Such an interaction, which destabilises the carbanion centre, should be distinctly weaker for position 3 and for a heavier heteroatom, owing to a higher diffusivity of the orbital. The difference between CH-acidities in the position 2 of five-membered heterocycles is rather low, (1-2 pKa units). The introduction of the (-M) acetyl group raises the acidities only slightly.

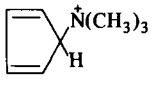


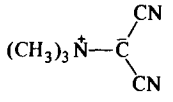
pKa 33[276]

Thus, the difference in pKa between methyl -3 acetylindole and the unsubtituted indole is only about 2 units, on the other hand acetylation of methane raises the acidity by about 30 pKa units. This may be explained by assuming that in the acetylindole anions the p-orbital bearing the negative charge cannot conjugate with the carbonyl group and the acetyl group inductive effect only operates, whereas, the anion $CH_3COCH_2^-$ is planar and the negative charge is localised principally on the oxygen atom. Thus, acetyl groups raise the stabilities of the heterocyclic carbanions under discussion by about 2 pKa units via its inductive effect.

5. Onium Compounds. Inductive Effect. d-Orbital Effect.

Tetramethylammonium iodide gives a metalation product when acted upon by phenyllithium[251], indicating that the ion $(CH_3)_4N^+$ is a stronger acid than is benzene. The Cram[2] pKa for tetramethylammonium ion is 33 units. Cram assumed that trimethylammoniumylide is stabilised because the electron pair occupies an orbital having a higher s-character than even an sp^3 orbital has, and thus favours the drawing together of the opposite charges. When strong acidifying substituents are attached to the carbon atom the nitrogen ylides are stabilised so efficiently that they become zwitterions soluble in water and melt at a high temperature. Two examples are shown below.





pKa 10.06 in water[252], m.p. 153[253]

The acidities of onium salts as a function of the heteroatom may be arranges as follows: (pKa's in aqueous solutions in parenthese[254]).

$Me_3\overset{+}{N}CH_2COPh$ (~10.5)

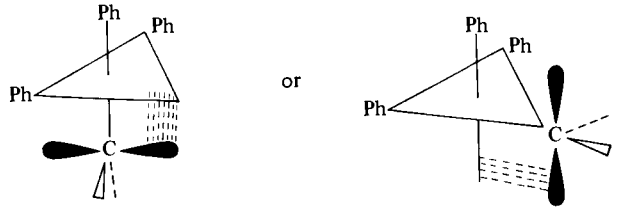
$Me_3\overset{+}{P}CH_2COPh$ (9.2)

$Me_3\overset{+}{A}sCH_2COPh$ (9.15)

$Me\overset{+}{S}CH_2COPh$ (8.25)

Evidently, the stabilities of the ylides rise from the left to the right in a Period, from nitrogen to phosphorus in a Group. This agrees with the data published by Issleib and Lindner[255] and by Johnson et al[256-257]. The phosphonium pKa values are close to, but usually below, the values for the respective arsenic compounds.

This rightward increase in acidity in a Period may be assigned to the increase in electronegativity (As 2.0, P 2.1, S 2.5; Pauling's values) and, correspondingly, in the onium group (-I) effect. The stabilisation observed on going from nitrogen to phosphorus (and arsenic) has been explained by d-orbital effects[252]. Phosphorus acquires electrons on its vacant 3d orbital from the negative 2p orbital of the stable ylides, which is usually pictured in the following way[252].



(A Phosphorus atom is in the centre of each of the triangles.)

Two phosphonium groups stabilise the anionic charge so strongly that bis(triphenylphosphonium)methane becomes a di-acid[258].

$$Ph_3\overset{+}{P}\text{-}CH_2\text{-}\overset{+}{P}Ph_3 \overset{pKa\ 5.60}{\rightleftharpoons} Ph_3\overset{+}{P}\text{-}\overset{-}{C}H\text{-}\overset{+}{P}Ph_3 \rightleftharpoons Ph_3\overset{+}{P}\text{-}\overset{-}{\overset{-}{C}}\text{-}\overset{+}{P}Ph_3$$

The effects of substituents in the organic group are illustrated in Table 33. The first two series (Series 1 and 2, Table 33) obey the Hammett equation (ρ is -2.66 for P, -2.38 for As). The effect of the group X on stability of $XCOCH{=}PPh_3$ (Series 3) may be mainly due to mesomeric effects because (-I and +M) substituents destabilise the ylides proportionally to their (+M) effect ($NH_2 > CH_3O$). The inductive effect, however, is also quite significant: the

chloroacetonyl salt is 2 pKa units more acidic than is the unsubstituted acetonyl compound.

TABLE 33

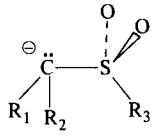
Substituent effect on Acidities of Phosphonium and Arsonium Salts at 25°C

1. para-Substituted phenacyltriphenylphosphonium salts, $Ph_3\overset{+}{P}CH_2COC_6H_4X$-p[259], EtOH/$H_2O$ 1/1 at 25°			
X	pKa	X	pKa
MeO	6.90[123 168 260]	Cl	5.50
CH_3	6.54	B	5.48
H	6.20 (6.0[260])	NO_2	4.11 (4.2[260])
2. para- Substituted phenacyltriphenylarsonium salts $Ph_3\overset{+}{A}sCH_2COC_6H_4X$-p[261], EtOH/$H_2O$ 1/1			
MeO	9.16	Cl	8.02
CH_3	8.97	Br	7.95
H	8.52	NO_2	6.67
3. Onium salts leading to the stable ylides $XCOCH{=}PPh_3$[260]			
NH_2	11.0	CH_3	6.6
CH_3O	8.8	$ClCH_2$	4.5
4. Onium salts leading to the stable ylides $Ph_3P{=}C(X)COPh$[262], in methanol			
H	6.0	Br	5.0
I	5.9	Cl	4.3

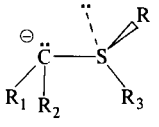
The pKa values for the last four compounds of Table 33 give witness to the fact that ylide stabilities rise with inductive effect in the series I<Br<Cl. On the other hand, spatial factors cannot be ruled out either, e.g. the large iodine atom may hinder the formation of a planar carbanion.

6. Sulphones. gauche-Effect.

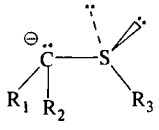
In sulphones (I), sulphoxides (II), sulphides (III) and sulphonium salts (IV), there exists a rather high energy barrier preventing rotation around the C-S bond (in non-planar carbanions there is also a barrier to inversion). The compounds can, therefore, give optically active products, unlike other systems that give only racemic products under the same conditions (see[263] for a review).



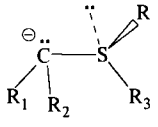
(I)



(II)



(III)



(IV)

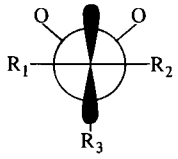
The stereochemistry of compounds similar to I to IV containing a neutral nitrogen atom with a lone pair (e.g., sulphamides, sulphineamides, sulpheneamides, hydrazine) rather than a negative carbon lead to the following stereochemical regularities predictable in I to IV[264]

(i) Interaction such as electron pair/electron pair, electron pair/polar bond (S-O), polar bond/polar bond raise the rotation-inversion barrier, and

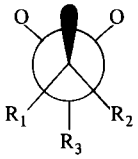
(ii) the most stable is the conformer in which the maximal possible number of electron pairs and polar bonds is in the gauche-conformation.

Calculations for α-sulphonyl, α-sulphinyl and α-sulphenyl carbanions along the lines proposed by Wolfe[265] predict that highest stability corresponds to the maximal gauche-effect.

The most stable conformer of the planar α-methylsulphonyl anion is structured as V [269 270], while the respective pyramidal carbanion prefers the structure VI. In both anions the carbanion electron pair is directed along the bisector of the O-S-O angle.



(V)



(VI)

These calculations state that for $R_1 = R_2 = R_3 = H$ the anion VI should be 2.4 kcal/mole more stable than anion V[266], but experiment shows that an increase in the α-sulphonyl carbanion planarity does not decrease the racemisation barrier[271]. Base-catalysed deuterium exchange in 1-phenethyl phenyl sulphone is faster by a factor of 10^4 than it is in 2-octyl phenyl sulphone. Consequently, the carbanion centre in the former compound is more sp2-hydridised (owing to conjugation with the phenyl group). However, the racemisation barrier is higher in the phenethyl carbanion than it is in the

octyl anion. Thus, no preference in favour of anion V or VI may be given as yet.

The most acidifying of the groups under discussion is sulphonyl and it is profitable to focus attention on the relationship between geometry and equilibrium acidity in sulphones. Sulphoxides as acids are too weak and data on their pKa's is rather scarce. The stereochemical aspects of kinetic acidity of sulphur-containing compounds are better understood and the discussion of asymmetrical carbanions will be further discussed in Chapter IV dealing with stereochemistry of proton transfer.

TABLE 34

Acidities of Cyclic Disulphonyl Methanes in Water at 25°[272].

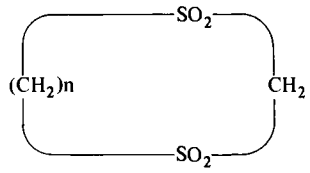
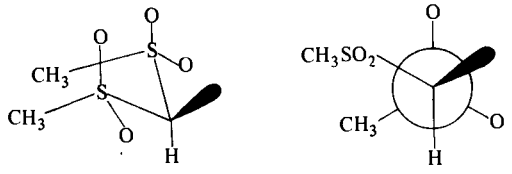
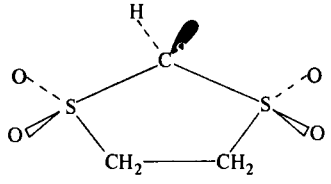
Compound	n	pKa
	2	13.9
	3	12.61
	4	11.75
	5	10.99
$CH_2(SO_2CH_3)_2$	-	12.50

Table 34 lists pKa values for a number of cyclic disulphonyl methanes[272]. The acyclic sulphone has a pKa of 12.5. It may very well acquire a conformation in which gauche-effect operates at its maximal (VII) (on the right is the Newman projection for one of the C-S bonds).

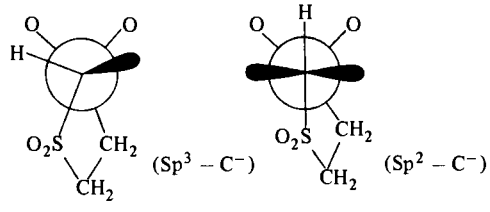


(VII)

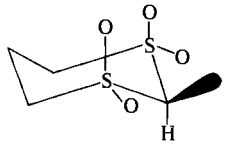
For the five-membered cyclic sulphone, no gauche-conformation is possible in the carbanion (VIII) whether the negative orbital be sp^3- or sp^2-hybridised, so the sulphone is a weaker acid compared with the acyclic compound.



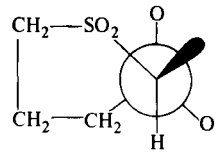
VIII



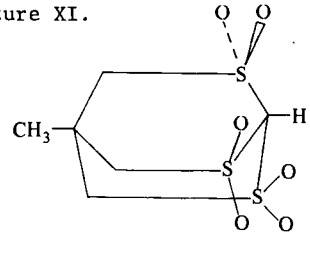
In the six-membered cycle (IX), the gauche-effect is as efficient as it is in the acyclic sulphone, and the pKa values of the compounds are close (Table 34).



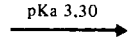
IX

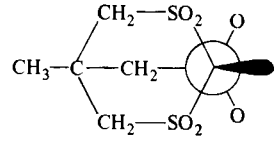


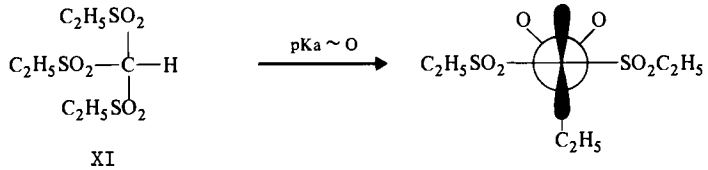
The higher stability of the planar structure V compared with that of the pyramidal structure VI (see above) makes it clear why the tricycle structure X is a weaker acid[28] than is the acyclic tris(ethylsulphonyl)methane structure XI.



X







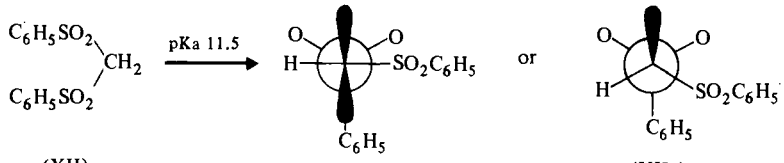
XI

In both cases the gauche-effect is possible, but in the first case X the rigid configuration fixes the sp^3 hybridisation of the orbital bearing the negative charge.

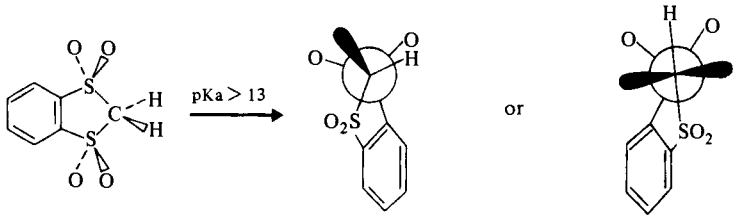
Breslow and Mohacsi[273] synthetised the compounds XII to XV, measured their pKa's and found an interesting acidity pattern. When the carbanion was generated in the α-position with respect to the carboethoxy group the cyclic compound was more acidic, whereas when no carboethoxy group was present in the molecule the acyclic compound was the stronger acid.

The fact that diphenylsulphonylmethane XII is more acidic than is the cyclic sulphone XIII may be explained by assuming that gauche-effect is at its maximal in the former compound; the rigid XIII cannot acquire a conformation in which electrostatic interactions would be maximally favourable (cf. XIIa and XIIIa, and pKa XII<pKa XIII. Gauche-effect alone, however, does not explain why pKa XIV > pKa XV. The XIVa conformation is more favourable compared with XVa, so the opposite sequence seems expectable. Cram introduced solvation of anions as a reason for the "abnormal" pKa sequence. He believed[2] that the higher acidity of XV was because solvation of the cyclic anion was less hindered than was that of the acyclic one.

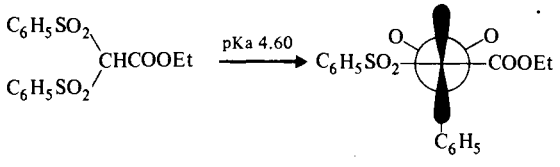
The polar effects on sulphone acidities have been studied by Amel and Marek[275] Arylsulphonyl acetophenones were titrated in 0.1M potassium hydroxide in 95% ethanol to show that substituents in the ring bonded with the SO_2 group affect the acidities somewhat more than do substituents in the benzene ring adjacent to the carbonyl group. It is interesting to note that a p-carbomethoxy substituent in the group COPh (Table 35) increases the acidity (similarly to the case of halogens) whereas the same substituent introduced in the para-position of the $PhSO_2$ benzene ring lowers it.



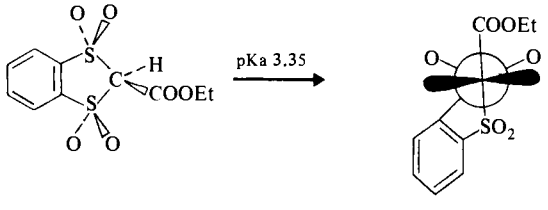
(XII) (XIIa)



(XIII) (XIIIa)



(XIV) (XIVa)

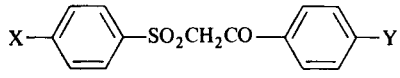


(XV) (XVa)

TABLE 35

Substituent Effect on Acidities of Substituted Arylsulphonyl Acetophenones, in 95% EtOH-KOH[275].

pKa	X(Y=H)	ΔpKa		Y(X=H)	pKa
10.97	H			H	10.97
10.33	Br	-0.66	-0.53	Br	10.44
10.52	Cl	-0.45	-0.44	Cl	10.53
10.80	F	-0.17	-0.07	F	10.90
11.42	OCH_3	+0.45	-0.17	OCH_3	10.70



Chapter III

Kinetic CH-Acidity

The method of studying lower CH-acidities based on the measurement of rates of base-catalysed hydrogen isotope exchange[277] is used extremely widely and has produced a wealth of data on mechanisms, stereochemistry, effects of structure, solvent, catalyst, of ion-pair formation etc.

The most extensive studies on hydrogen isotope exchange have been made by Shatenshtein's and Streitwieser's teams and their work is discussed in detail in this Chapter.

I. Hydrogen Isotope Exchange. .Protophilic Mechanism.

Kinetic acidity is characterised by the rate of proton abstraction from a CH-acid acted upon by base. Kinetic and equilibrium acidities often vary in parallel with each other, i.e. the Brönsted equation is valid[278].

$$\lg K_1 = -\alpha.pKa + const. \qquad (1)$$

where α is the Brönsted coefficient (usually $o < \alpha < 1$) and k_1 the rate constant of the reaction $R\text{-}H+B^- \rightarrow R^- + HB$.

Hydrogen exchange reactions involve two successive proton (or D^+ or T^+) transfer steps, from the CH-acid to the base and from the protonated base to the carbanion:

$$RD + B \underset{k_1}{\overset{k_1}{\rightleftharpoons}} K^- \ldots DB \xrightarrow[HB]{k_2} R^- \ldots HB \longrightarrow RH + B^- \qquad (2)$$

In this sequence the exchange catalyst B^- is a weaker base than is the carbanion R^-. This mechanism has been termed protophilic[277].

The step k_2 corresponds to isotope exchange in the encounter complex. The catalyst is usually a base conjugate to the solvent containing a hydrogen isotope different from that in the CH-acid under study. Thus, the scheme (2) shows the exchange reaction of a CH-acid with the deuterated solvent DB, catalysed by the base B^-. Since $[DB] >> [RH]$, the step k_2 may be though of as kinetically irreversible. The discussion below is based on the steady--state principle throughout.

In terms of this principle ($k_1 << k_{-1}$), the observable rate constant is

$$k_{obs} = k_1k_2/(k_1 + k_2). \qquad (3)$$

When $k_2 >> k_{-1}$ then k_{obs} approximately k_1 and the exchange rate is governed by the rate of proton abstraction from the CH-acid under the action of the base.

When $k_2 << k_{-1}$ then k_{obs} approximately Kk_2, where $K = k_1/k_{-1}$ and the exchange

rate is governed not only by the proton abstraction step. Note that $-\lg K$ = pKa (RH) - pKa (HB).

The question as to which of the hydrogen exchange steps is rate-determining may be answered by studying for example, the primary kinetic isotope effect (KIE). If KIE is sufficiently high then it can be taken as very likely that hydrogen abstraction will be rate-determining.

Thus, the isotope effect of the deuterium for tritium exchange in toluene -α-t is k_D/k_T = 2.8 to 3.0[279] for a cyclo-$C_6H_{11}NH_2$-cyclo-$C_6H_{11}NDLi$ system, whence the Swann equation[280] gives a k_H/k_D value of 10 to 12.

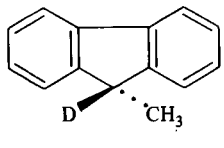
$$k_H/k_D = \frac{1}{(k_D/k_T)^{2.26}} \qquad (4)$$

So a high KIE means that the extent of C-H bond rupture is very high in the transition state, that is, the k_1 step is rate-determining.

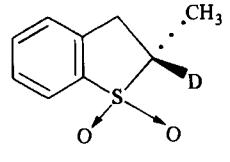
On the other hand, KIE is close to unity for CH-acids (including toluene) in the dimethylsulphoxide-potassium tert butoxide system[281]. The low KIE value may be explained by assuming that $k_2 \ll k_1$ ("internal return mechanism"[282]) and, therefore, $k_{obs} = (k_1/k_{-1})k_2 = Kk_2$ (equation 2), KIE should be close to unity for the step k_2 while values for the reactions k_1 and k_{-1} are comparable, hence the observable k_H/k_D value is close to unity.

Similarity between a hydrogen exchange reaction (kinetic acidity) and the CH-acid ionization equilibrium (equilibrium acidity) is governed by the rates ratio of the reactions k_{-1} and k_2 (equation 2). This ratio shows how closely the isotope exchange rate depends on the proton transfer rate. This may be exemplified as follows.

Cram studied the stereochemistry of proton transfer from 2-N, N-dimethylcarboxyamido-9-methylfluorene I in a methanol-potassium methoxide system[283] or from 2-methyl-2,3-dihydrobenzothiophene 1,1-dioxide II in a tert butanol-potassium-tert butoxide system at 25°[284].



I pKa ca 20

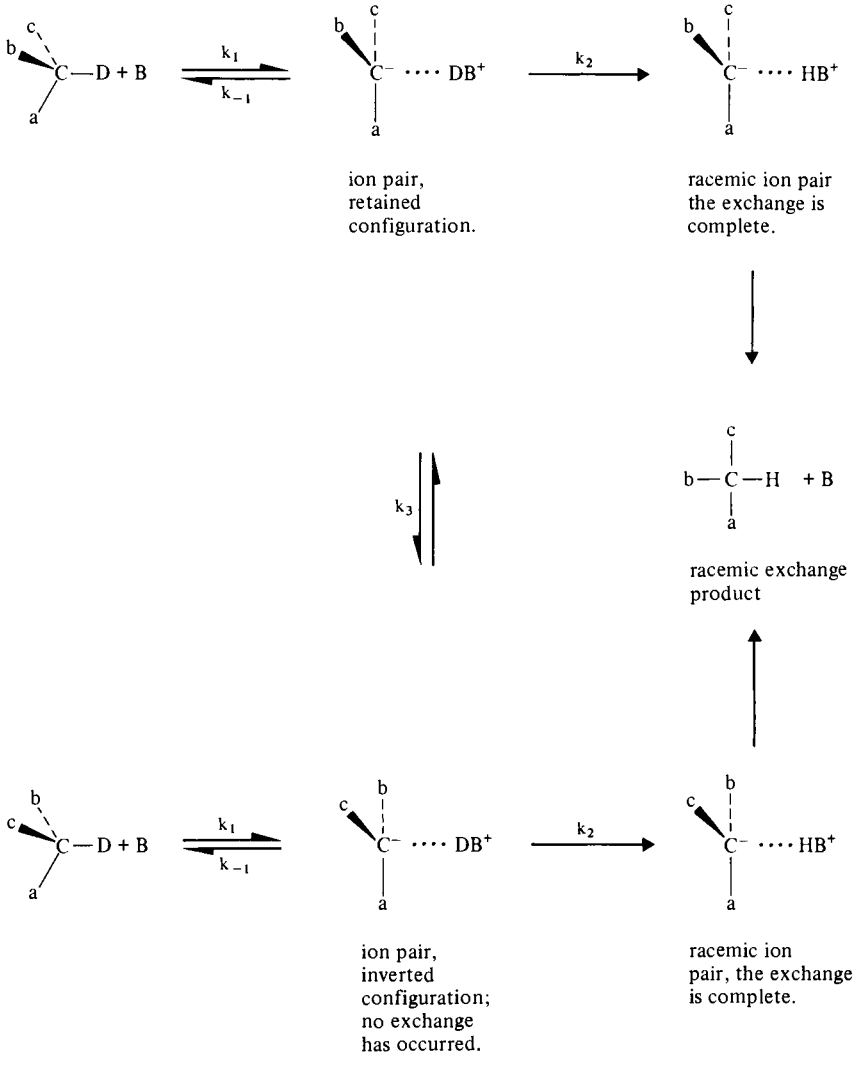


II pKa ca 23

Stereochemically the reactions may be written as shown overleaf.

The scheme demonstrates that the hydrogen exchange is accompanied by racemisation* occuring at the ion-pair ($R^-....HB^+$ or $R^-.....DB^+$) formation

*Inversion or retention have been observed in other systems, see Chapter IV for details.

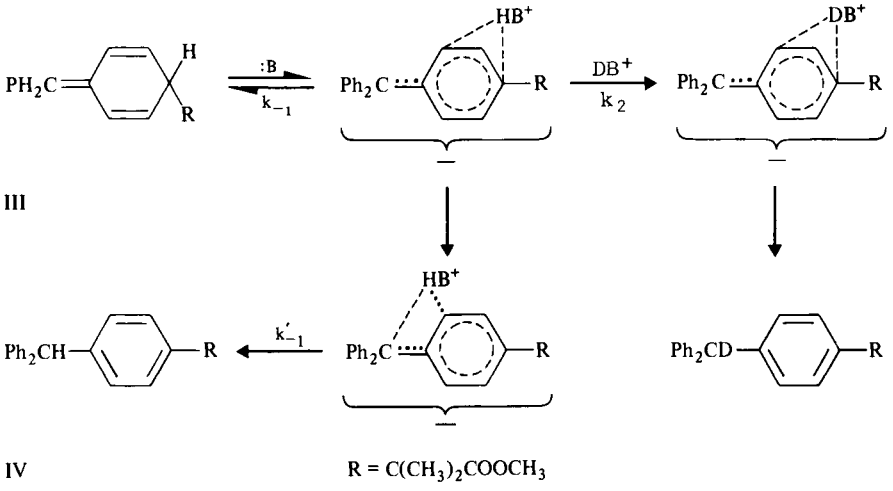

b
c
a
C—D + B
k_1
k_{-1}
C⁻ ···· DB⁺
k_2
C⁻ ···· HB⁺
ion pair, retained configuration.
racemic ion pair the exchange is complete.
k_3
b—C—H + B
racemic exchange product
ion pair, inverted configuration; no exchange has occurred.
racemic ion pair, the exchange is complete.

step. The process that leads to inversion of the initial CH-acid at the ion-pair ($R^-.....DB^+$) step, k_3, is termed isoinversion.

When the isoinversion rate is sufficiently high the exchange may lead to complete racemisation (referred to as isoracemisation[284]).

The isoinversation → isoracemisation phenomenon has been observed with a great number of hydrogen exchanges. A study of the phenomenon allows one to estimate the ratio of the carbanion protonation rate (k_{-1}) to the rate of isotope substitution in the encounter complex, k_2. Isotope analysis of the exchange products of I (2-N,Ndimethylcarboxyamido-9-methylfluorene)[283] in a methanol-potassium methoxide system showed that the isoracemisation rate is 4% of the total exchange rate[285]. Isotope exchange in the compound proceeds via two parallel routes designated by $k_1 + k_2$ and by $k_1 + k_3 + k_2$. The protonation rate constant is $k_1 = 9 \times 10^3$ $l\text{-mole}^{-1} \times \text{sec}^{-1}$ for the 9-methylfluorenyl anion in methanol[286]. If it is assumed that k_1 for compound I does not differ significantly from this value, then the ratio $k_1/k_2 = 0.04$, valid when the step $k_1 + k_3 + k_2$ operates, will give a value of k_2 of 10^5 to 10^6 $l\text{-mole}^{-1}$ sec^{-1}. This is the upper limit for k_2 since the exchange occurs also via the path $k_1 + k_2$. Consequently, the isotope substitution rate in the encounter complex, k_2, is lower than the diffusion rate.

A study of the intramolecular prototropic transformation of III into IV shows that the carbanion protonation rate may be equal to the DB for HB substitution rate in the encounter complex[287].



IV

The deuterium-free product yield is 47% in a methanol-sodium methoxide system and 50% in a tert butanol-sodium tert butoxide system. The conclusion is that the ROD for ROH substitution rate (k_2) in the reaction complex is comparable to the protonation rate of the respective triphenylmethyl anion.

Neither k_2 nor k_{-1} are diffusion-controlled in the above example. This has

been demonstrated further by Russell et al[288] and by Guthrie[289] who generated triphenylmethyl anion from triphenylmethane, in a butanol-potassium tert butoxide system containing nitrobenzene, and shows that the anion transfers one electron to a nitrobenzene molecule and is transformed into a triphenylmethyl radical. The electron transfer (k_e) and the proton transfer (k_{-1}) occur in parallel.

$$Ph_3CH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ph_3C^- \quad \begin{matrix} \xrightarrow{k_{-1}} Ph_3CD \\ \xrightarrow{k_2} Ph_3C \end{matrix}$$

with k_e/k_{-1} being equal to 720. If it is assumed that the electron transfer rate is diffusion-controlled, then the Ph_3C^- protonation rate in tert-BuOD will be some three orders less than is the diffusion rate. Thus, carbanion protonation rates, even when the carbanions are very strong bases, may be below the diffusion control range.

The examples discussed above allow one to come to the conclusion that the rate of base catalysed hydrogen isotope exchange in CH-acids is not always a measure of their intrinsic kinetic acidity. Thus, with the internal return mechanism ($k_2<k_{-1}$), the isotope exchange rate in triarylmethane is not a characteristic of kinetic acidity because k_2 values may differ for different compounds of the series.

II. Hydrogen Isotope Exchange Rates in CH-Acids of Various Types

1. Hydrocarbons

Shatenshtein[277] was the first to show that alkanes are capable of hydrogen/deuterium substitution when heated in liquid deuteroammonia containing potassium amide at 100°C for several days. Streitwieser employed lithium or caesium cyclohexylamide solutions in anhydrous coclohexylamine as strongly basic media[290,291].

a. Alkanes and cycloalkanes

Alkanes and cycloalkanes are the weakest CH-acids known and hydrogen isotope exchange in these compounds is rather slow.

Shatenshtein et al[292-294] showed that in an NH_3-KNH_2 system at 25°C, benzene, hexene, and cyclohexene exchange their hydrogen for deuterium whereas cyclohexane does not.

Kinetic acidities of a great number of cycloalkanes, $(CH_2)_n$,n=3 to 14, have been studied by Streitwieser and his team[295] and by other workers[296]. The results are summarised in Table 36. A rather high value of KIE (kinetic isotope effect) (k_H/k_D 6.5) was observed for hydrogen exchange in cyclohexane demonstrating that the internal return mechanism is insignificant in this case. In other words, the exchange rate is, probably, controlled by the step k_1 (eq. 2). Streitwieser et al[295] and Closs and Larrabee[298] observed a good linear correlation between logarithmic relative exchange constants and the $J(^{13}C\text{-}H)$ constants in cycloalkanes (n was 3 to 8), proving that kinetic acidity in cycloalkanes is mainly due to s-character of the C-H exocyclic bond.

Kinetic acidity measured using caesium cyclohexylamide for the cycloalkanes (n>6) is somewhat lower than is the cyclohexane acidity, however, the $J(^{13}C\text{-}H)$ values tend to a decrease thus indicating a decrease in the C-H bond s-character. The carbanion intermediate was assumed to have a pyramidal structure[295].

TABLE 36

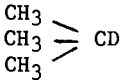
Relative H/T or H/D Exchange Rates in Cycloalkanes

	k_{rel} (H/T, vs. benzene)		
	CsCHA/CHA at 50°C[295]	CsCHA/CHA at 100°C[295]	CsCHA/CHA at 50°C[296]
(Benzene)	(1.00)	(1.00)	(1.00)
Cyclopropane	7.70×10^{-4}	-	10^{-3}
Cyclobutane	3.1×10^{-7}	-	10^{-6}
Cyclopentane	6.3×10^{-8}	-	-
Cyclohexane[a)]	1.1×10^{-8}	1.1×10^{-8}	10^{-8}
Cycloheptane	8.3×10^{-9}	8.3×10^{-9}	-
Cyclooctane	7.0×10^{-9}	7.0×10^{-9}	-
Cyclononane	-	1.1×10^{-8}	-
Cyclodecane	-	8.0×10^{-9}	-
Cycloundecane	-	6.6×10^{-9}	-
Cyclododecane	-	5.3×10^{-9}	-
Cyclotetradecane	-	3.8×10^{-9}	-

a) $k_H/k_T = 6.5$[297]
CsCHA = caesium cyclohexylamide
CHA = cyclohexylamine

Methane exchanges its hydrogen for deuterium in the caesium cyclohexylamide-cyclohexylamine system at 50°C about 310 times more slowly than does cyclopropane, but 2,200 times faster than cyclohexane[299]. In ethane, neopentane, and hexamethylethane, the primary C-H bond reacts 10^2 to 10^3 times slower than in methane[299]. Shatenshtein found[300 301] that in isobutane in an NH_3-KNH_2 system, only the primary hydrogen is exchanged.

exchange observed



no exchange observed

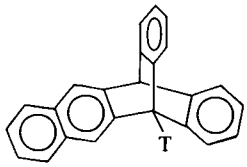
These data allow one to arrange aliphatic C-H bonds in the following reactivity series.

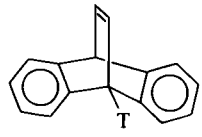
CH_4>primary -CH>secondary -CH>tertiary -CH

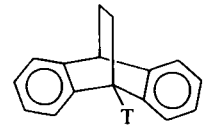
Alkanes and cycloalkanes, although they exchange their hydrogens rather slowly, may have some structural peculiarities which are capable of increasing even the cycloalkane C-H bond acidity significantly. Thus, the kinetic acidity of the bridgehead hydrogen in triptycene (k_D/k_H 2.2) is about four times lower than the benzene kinetic acidity[302 303].

The high kinetic acidity of triptycene may be quantitatively interrelated with the s-character of the C-H bonds under ionisation and with the inductive field effect. The field effect may be approximated[291] by a sum Σ 1/r, of reciprocal distances between the carbon carrying the lone pair and each of the π-carbons of the system. Streitwieser and his coworkers[304]

showed that the exchange rate (caesiumcyclohexylamide-cyclohexylamine at 25°C) correlates with Σ 1/r for triptycene and for the compounds V, VI and VII.







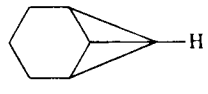
Relative rate: V 2.0 VI 0.20 VII 0.0013

(K_{rel} is 1.00 for triptycene)

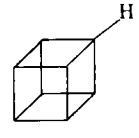
Σ 1/r, A^{-1}: 7.35 5.52 4.14

(Σ 1/r is 6.66 A^{-1} for triptycene)

Hydrogen exchange in VIII is very fast in a tert-butanol potassium tert-butoxide system[305], owing to a high C-H bond s-character. A value of 40% has been estimated from the nuclear magnetic resonance spectrum of this substance.



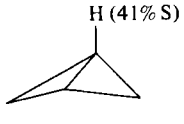
VIII

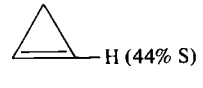


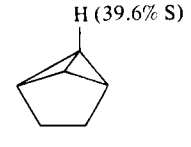
IX

The hydrogen exchange rate in cubane IX has a CH-bond s-character of 30 to 32% which is higher than is the rate in benzene[296].

Probably, a higher rate of exchange may be expected in the following strained structures (in parentheses are C-H s-characters[123].).







b. Alkenes

Norbornadiene is metalated by butyllitium in the vinyl position only[306 307]; consequently, the vinyl protons are more acidic than are the alicyclic ones.

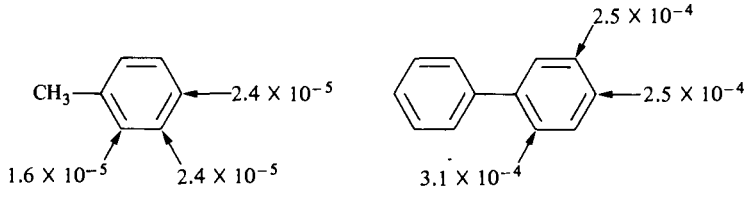
The $J(^{13}C\text{-}H)$ values and other data suggest that the vinyl C-H bonds have a greater s-character compared with the aliphatic bonds; therefore, ethylene compounds should be more apt to undergo hydrogen exchange[300]. However, the more facile exchange may be due to allyl rearrangements (Chapter IV) transforming the vinyl protons to allyl protons. Thus, only seven hydrogens (five allyl and two olefine) of the sixteen hydrogens of 2,4,4-trimethylpentene-1 are exchanged in an NH_3-KNH_2 system at 120°C during 100 hours [293 300], whereas all the hydrogens may be exchanged in hexene-1 and cyclohexene.

The exchange rate of the four deuterium atoms in tetradeuteroethylene is only about 27% of that in monodeuterobenzene in caesium cyclohexylamide-cyclohexylamide. Consequently, the exchange rate in monodeuteroethylene is about 7% of that in monodeuterobenzene[309].

c. Arenes

Isotope exchange rates have been determined for many aromatic hydrocarbons in NH_3KNH_2[292-294,310-313] or in cyclohexylamine containing lithium or caesium cyclohexylamides[314-318].

Shatenshtein et al[313] showed that the deuterium exchange rates measured for ortho-, meta-, and para-deuterotoluenes in liquid ammonia at 25°C are rather close to each other (k_1 values (sec^{-1}) are listed below (in 0.02 M potassium amide).



This may be explained in the following way. In amide-catalysed exchanges the attack is directed on hydrogen, unlike electrophilic or nucleophilic aromatic substitutions in which the reaction site is carbon. Consequently, the negative charge built up on the carbon cannot interact with the pi-system and resonance effects play a minor part as compared with the inductive and field effects.

The effect of other substituents upon the rate of phenyl hydrogen exchange is summarised in Table 37[308,326].

The data of Table 37 demonstrate that the accelerating effect of substituents such as F, PhO, or CH_3 decreases with the distance between the reaction site

and the substituent. Also, relative exchange rates measured for the ortho-positions correlate well with inductive δ_1 constants[308] and ρ is as high as 11. Conseuqnetly, inductive and field effects play a leading part in the charge stabilisation.

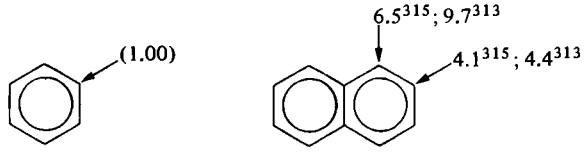
TABLE 37

Substituent Effect upon Relative Rates of Hydrogen Exchange in the Benzene Ring[308 326].

Substituent X	Relative rate (Benzene = 1)		
	ortho	meta	para
F	10^6	10^3	10^2
CF_3	10^5	10^4	10^4
PhO	10^4	50	4
MeO	500	1	0.5
MeS	330	24	6
Ph	5	3	3
Me_2N	1.4	0.2	0.07
CH_3	0.14	0.32	0.23
H	(1.00)	(1.00)	(1.00)

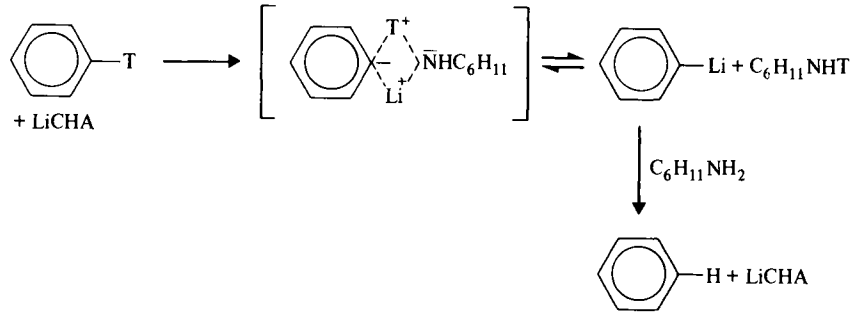
The primary kinetic isotope effect found for tritiated benzene in cyclohexylamine containing caesium cyclohexylamide is $k_D/k_T = 2.5$[317] hence from equation 4 $k_H/k_D = 8$. In the presence of lithium cyclohexylamide, however, k_D/k_T is only 1.6,[315] and k_H/k_D is 2.8. A rather low KIE (kinetic isotope effect) in the latter case may be explained by assuming that the protophilic mechanism is accompanied or even replaced by the nucleophilic addition-elimination mechanism as shown below (B.).

The rate-determining step is nucleophilic addition followed by fast exchange of the allyl hydrogen[315]. The mechanism predicts a value of k_D/k_T of unity. Also, the alpha- and beta-hydrogens should exchange at an equal rate in naphthalene. The latter conclusion, however, disagrees with experiment.

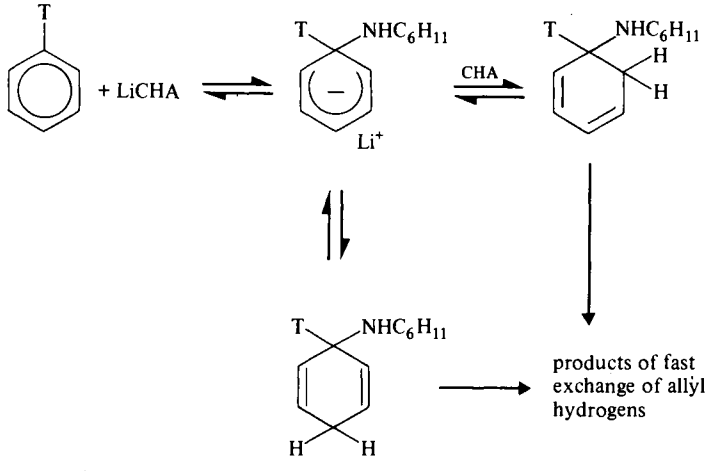


If, in the mechanism (B) the lithium cyclohexylamide abstraction rate is comparable with the exchange rate, then the higher rate will be observed for the alpha-position of naphthalene since the anion Xa should protonate faster than the anion Xb[315] This mechanism should lead to a small KIE

A:


T
+ LiCHA
T+
NHC6H11
Li
Li + C6H11NHT
C6H11NH2
H + LiCHA

B:


T
+ LiCHA
T
NHC6H11
Li+
CHA
T
NHC6H11
H
H
T
NHC6H11
H
H
products of fast
exchange of allyl
hydrogens

A B

Shatenshtein[319] believes that the second version of the mechanism (B) is possible because on going from an NH/KNH_2 system to a dimethylsulphoxide--potassium tert-butoxide system the increase in the hydrogen exchange rate in the side chain of methyl arenes is higher by a factor of 10^4 than the increase in the aryl hydrogen exchange rate (mechanism (B) is possible only with aryl hydrogen exchange).

The high isotope effect (k_D/k_T 2.5) observed in a benzene-cyclohexylamine-caesium cyclohexylamide system agrees with the protophilic mechanism. The contribution of the mechanism (B) is in this case probably low, owing to an increase in the exchange rate on going from lithium cyclohexylamide-cyclohexylamine to caesium cyclohexylamide-cyclohexylamine.

Comparison of absolute exchange rates in hydrocarbons showed that the caesium cyclohexylamide catalysed processes are $10^{3.5}$ faster than the lithium cyclohexylamide catalysed ones, e.g., the absolute rate constants found for tritiated benzene at 25°C are 5.0×10^{-2} 1/mole x sec (caesium cyclohexylamide) and 1.4×10^{-5} 1/mole x sec (lithium cyclohexylamide)[317].

TABLE 38

Relative Hydrogen Exchange Rates in Various Media

Hydrocarbon	LiCHA[318] T-exchange	CsCHA[318] T-exchange	KNH_2/NH_3[308] T-exchange
Benzene	(1.00)	(1.00)	(1.00)
Toluene (ortho)	0.12	0.20	0.22
Toluene (meta)	0.54	0.59	0.45
Toluene (para)	0.47	0.52	0.41
Cumene (α)	0.79	1.36	3
sec-Butylbenzone(α)	0.31	0.38	-
Mesitylene (ring)	-	0.013	0.015

CsCHA = caesium cyclohexylamide
CHA = cyclohexylamine

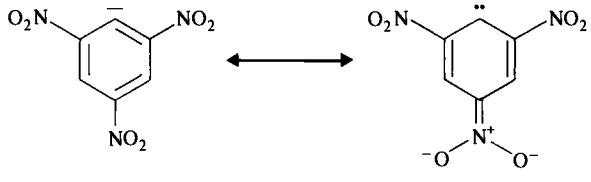
However, the relative rates do not differ much[318] (Table 38). The activation parameters of the exchange of aromatic hydrogens in these three systems are as follows.

	$\Delta H,^{\neq}$ kcal/mole	$\Delta S^{\neq}$ e.u.
Benzene-t caesium cyclohexylamide	13	-22
Toluene-2-t-caesium cyclohexylamide	15	-17
Benzene-d (KNH_2/NH_3)	15	-19
Naphthalene-2-d-lithium cyclohexylamide	12	-37

t = tritiated
d = deuterated

Normal bimolecular $\Delta S^{\neq}$ values are observed with caesium cyclohexylamide and KNH_2 whereas $\Delta S^{\neq}$ found with lithium cyclohexylamide is much more negative. Streitwieser et al[317] believe that this is due to additional solvation of lithium ion in the transition state. Lithium cyclohexylamide in solution in cyclohexylamine is in the form of the aggregates $((LiCHA)_n$, with n being 2 or 3)[320]. Solvent molecules are partially eliminated when these aggregates are formed from the monomers. On the other hand, lithium cyclohexylamide reacts in the form of monomeric ion-pairs[290]. The monomer formation is accompanied by solvation that is partially retained in the transition state.

The introduction of electron-withdrawing substituents into the benzene ring accelerates the rate of exchange, e.g., m-dinitrobenzene and 1,3,5-trinitrobenzene undergo the exchange with methanol in the presence of sodium methoxide[321]. The data in Table 39 show that the effect of nitro groups is explainable in terms of inductive effect rather than the "carbene resonance"[322],



since position 2 in 1,3-dinitrobenzene is 100 times as reactive as is position 4 or 6. The carbene resonance may, probably, also be done without in the case of diphenyl anion stabilisation.

TABLE 39

H/D Exchange Rates in CH_3OD/CH_3ONa at 75°C[321]

Compound	Position	k_2(1/mole sec)
1,3,5-Trinitrobenzene	2,4,6	0.795
1,3-Dinitrobenzene	2	1.55×10^{-2}
1,3-Dinitrobenzene	4,6	1.24×10^{-4}

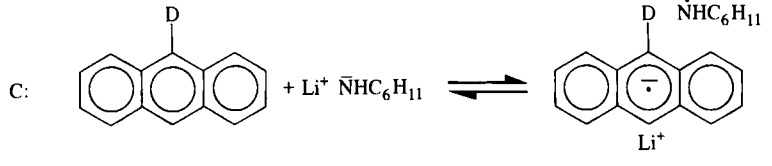
TABLE 40

Relative Deuterium Exchange Rates in Deuterated Aromatics[308,316,323,324].

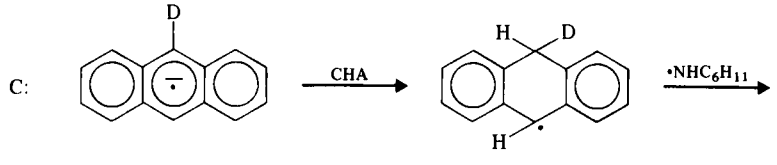
Compound	Position	k_{rel}		K_D/k_T
		LiCHA, 50°C	KNH_2, 25°C	
Benzene		(1.00)	(1.00)	1.6
Diphenyl	2	1.2	4.7	-
	3	3.7	3.3	-
	4	2.3	2.9	-
Naphthalene	1	6.5	9.7	1.7/41/
	2	4.1	4.4	-
Phenanthrene	9	17.9	-	-
Anthracene	1	10.9	-	-
	9	45	-	1.2
Pyrene	1	24.9	-	1.2
	2	20.9	-	-
	4	31.3	-	-

Relative hydrogen exchange rates in polycyclic hydrocarbons (Table 40) can be well understood in terms of the electrostatic field effect model[291,316], because a good correlation exists between the logarithmic exchange rates and the sum of reciprocal distances between the carbons carrying negative charge and each of the other pi-atoms of the molecule[291,316].

It is noteworthy that a low kinetic isotope effect is observed in the exchange reactions under discussion; it decreases with an increase in the number of condensed rings in the aromatic system (Table 40). Probably, alongside with the routes reflected in the schemes A and B (page 87), a one-electron transfer mechanism may operate, especially so in polycondensed aromatic compounds.



The radical anion formed may further exchange, for instance, as follows.



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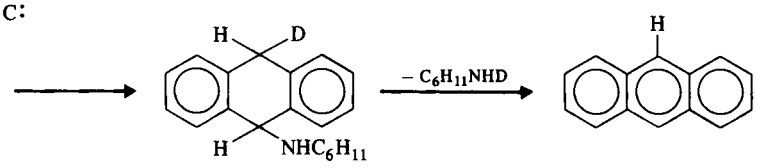


Radical anions have been proved to exist by Streitwieser and Lawler[316] in an aromatic hydrocarbon/cyclohexylamine/lithium cyclohexylamide system for anthracene and fluoranthene[316], although their formation might be due to a side reaction.

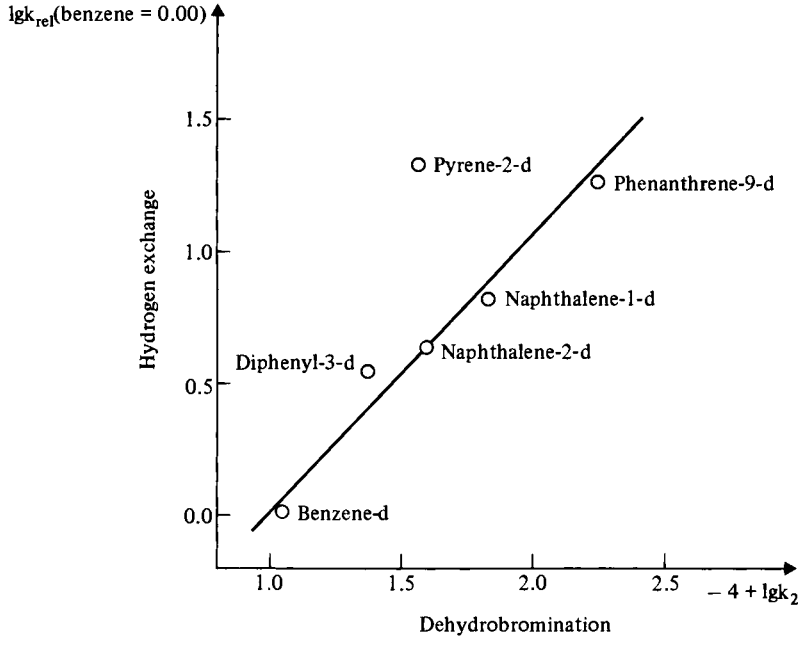
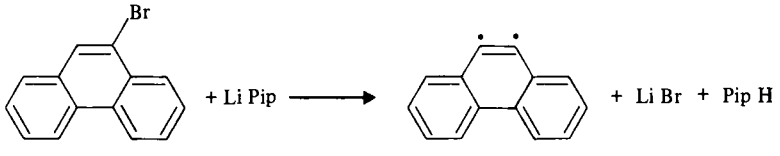


Fig. 9. Relative D/H-exchange rate (in cyclohexylamide/lithium cyclohexylamide at 50°C, Table 40) vs. dehydrobromination rate (in ether plus piperidine/lithium piperidide at 20°C)[325]

Figure 9 presents a correlation between the logarithmic exchange constants in aromatic hydrocarbons and the logarithmic dehydrobromination constants for the reaction aryl bromides with lithium piperidide[325] to produce arynes;



The pyrene value diverges from the straight line relationship shown in Fig. 9. The slow steps of hydrogen exchange and dehydrobromination may be very similar, but this does not allow one to choose between mechanisms A and B (P.87) and C (P.90/91).

d. Mono-, di-, and triaryl alkanes

alkyl benzenes

Hydrogen isotope exchange in the side chains of alkyl benzenes has been studied very extensively. The hydrogen atom in the alpha-position to the phenyl group is exchanged rather easily, so the compounds are convenient models to study the process. If the asymmetric benzyl carbon atom is present, the alkylbenzenes may be used for investigating the stereochemical pattern.

The second-order exchange rate constant is 6.70×10^{-3} l/mole x sec for toluene-α-d in a cyclohexylamine/lithium cyclohexylamide system at 50°C[290], Toluene-d or toluene-t with lithium cyclohexylamide in cyclohexylamine display no simple first-order kinetics with respect to the catalyst. The order varies from almost unity at a low concentration of lithium cyclohexylamide to approximately zero at high lithium cyclohexylamide concentrations[290,327]. This fits in well with the assumption that the real catalyst, lithium cyclohexylamide monomer, is in equilibrium with rather non-reactive dimer, trimer, and higher associates[320].

Primary kinetic isotope effect values (k_D/k_T measured under various conditions for toluene are in the range 2.8 to 3.0 in cyclohexylamine at 50°C [328], 2.3 to 2.5 at -25°C or 2.2 to 2.5 at 0°C in ammonia plus 0.05 M KNH_2 sys system[329] and 2.8 to 3.1 at 25°C in a CH_3SOCH_3/CH_3SOCH_2K system[330]. In a dimethylsulphoxide potassium tert-butoxide system, however, k_D/k_T for toluene is only 1.1 to 1.2[329,330] or even 0.8[338]. Cram and his team who studied isotope exchange in 2-phenylbutane in a dimethylsulphoxide/potassium tert--butoxide system also observed a rather low isotope effect (k_H/k_D 3; hence from equation 4 (P.79) k_D/k_T is 1.6). They employed the internal return exchange mechanism[282]. In a dimethylsulphoxide/potassium tert-butoxide system protons are probably supplied by tert-butanol whose concentration is so low that $k_{-1} > k_2$ [tBuOH],i.e., the internal return mechanism is favoured (cf. Section III).

The secondary deuterium isotope effect value for alpha-deuterium in toluene is $3k[PhCH_2D]/k[PhCD_3] = 1.31$ in a lithium cyclohexylamide-cyclohexylamine system at 50°C, it is 1.11 for ethylbenzene[332]; consequently, lithium and the deuterium which is split off may lie closely to the carbon atom in the transition state[332].

Table 41 lists relative exchange rates for substituted toluenes in strongly basic systems. For the reaction of unsubstituted toluene with lithium cyclohexylamide $\Delta H^{\neq}$ is 9 kcal/mole and $\Delta S^{\neq}$ is -39 e.u.

The exchange in ring-substituted toluene is accelerated by electron-withdrawing substituents and decelerated by electron-releasing substituents. In cyclohexylamine, the Hammet σ ρ correlation is an excellent straight line with a slope of -4.0[192].

This ρ value is much more negative than that found for the dissociation of phenols in water (ρ = -2.11); hence, the transition state is of a carbanion type. The electron-donor m- and p-alkyl groups decelerate the reaction, as expected, but the ortho-methyl effect is anomalous. Its polar effect should

be at least equal to the p-methyl effect[291] while the spatial hindrance to coplanarity of the methylene group with the ring in the transition state should decelerate the reaction even more. The observed constant, however, is not lower than, but is twice as high as that found for p-xylene. The assumption is that a decrease in rotational entropy is playing a role[192]. In the reactions of toluene derivatives which do not contain substituents in positions 2 and 6, the free rotating methyl group is transformed to a less rotative methylene group in the transition state. Methyl rotation in o-xylene is difficult, therefore, the higher hindrance due to the transformation to the methylene species is not so important.

TABLE 41

Relative Exchange Rates in Substituted Toluenes, $RC_6H_4CH_2D(T)$ and $C_6H_5CHXD(T)$

Compound	KND_2ND_3 at 100°[312, 313]	LiCHA/CHA at 50°[192, 333-5]	DMSO/t-BuOK at 25°[336]
1. Toluene substituted in the ring			
Toluene-α-d	(1.00)[a]	(1.00)[b]	(1.00)[c]
m-Trimethylsilyltoluene		1.01[d]	
p-Trimethylsilyltoluene		4.57[e]	
o-Xylene		0.60	1.4
m-Xylene		0.60	0.51
p-Xylene		0.31	0.033
o-Isopropyltoluene		0.41	
m-Isopropyltoluene		0.61	
p-Isopropyltoluene		0.29	0.023
1,2,4-Trimethylbenzene			0.26
1,3,5-Trimethylbenzene			0.22
1,2,3-Trimethylbenzene			1.12
1,2,4,5-Tetramethylbenzene			0.018
1,2,3,5-Tetramethylbenzene			0.12
1,2,3,4-Tetramethylbenzene			0.46
Pentamethylbenzene			0.056
Hexamethylbenzene			0.010
o-Ethyltoluene			0.51
m-Ethyltoluene			0.24
p-Ethyltoluene			0.026
p-tert-Butylbenzene			0.033
o-Fluorotoluene		12	
m-Fluorotoluene		22	
p-Fluorotoluene		0.73	
m-Trifluoromethyltoluene		60	
p-Trifluoromethyltoluene		ca.180	
m-Methoxytoluene		2.1	
p-Methoxytoluene		0.091	
2. Toluenes substituted in the side chain			
Toluene	(1.00)	(1.00)	(1.00)
1,2-Diphenylethane		0.50	
Ethylbenzene	0.14	0.12[f]	0.22

TABLE 41 *continued*

Compound	KND_2ND_3 at 10°	LiCHA/CHA at 50°	DMSO/t-BuOK at 25°
n-Propylbenzene		0.059g)	
iso-Butylbenzene		0.010h)	
Neopentylbenzene		0.006	
sec-Butylbenzene		0.0031i)	
Cumene	0.03	0.008	0.023
Benzene	0.014	0.005-0.010	ca.10^{-6}

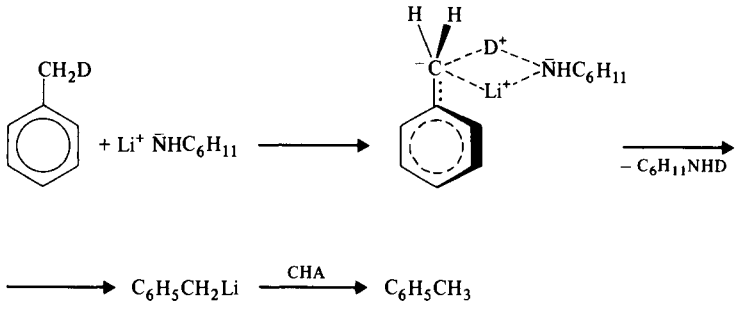
a) $k_2 = 1.4 \times 10^{-3}$ $M^{-1}sec^{-1}$.
b) $k_2 = 6.7 \times 10^{-3}$ $M^{-1}sec^{-1}$.
c) $k_2 = 6 \times 10^{-4}$ M^{-1} sec^{-1}; all the k_2 values are for toluene-α-d.
d) $k_D k_T = 3.3$
e) $k_D/k_T = 3.0$
f) $k_D/k_T = 2.39$
g) $k_D/k_T = 2.48$
h) $k_D/k_T = 2.87$
i) $k_D/k_T = 2.7$ with CsCHA at 25°[317].

The deviation from the Hammett plot is at its greatest for the p-fluorine substituent. The introduction of a fluorine atom at the para position in toluene slows down the exchange (Table 41) rather than accelerates it, and this is in disagreement with the assumption based on the positive δ value. The deceleration may be due to "anticonjugation" of the lone pair with the carbanion spearhead (cf. Section 2, Chapter II). The ortho- fluorine atom is also conjugated with the reaction site but, since it is close to this site, the inductive effect prevails and the ortho-fluorine atom increases the rate although it does this less effectively compared with the "non-anticonjugable" meta-fluorine atom.

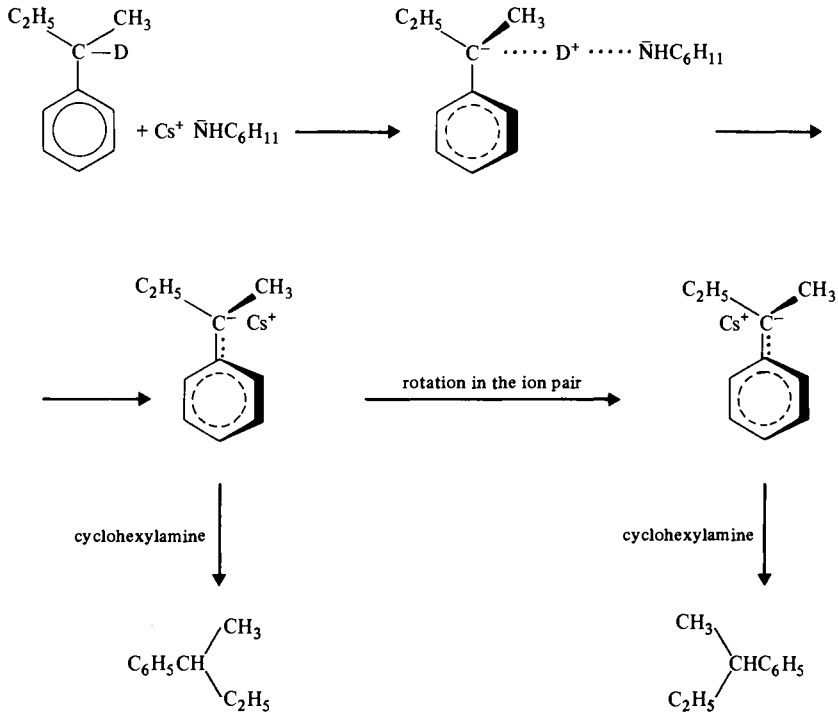
Relative exchange rates measure in cyclohexylamine or in liquid ammonia differ markedly from those measured in dimethylsulphoxide, this is especially so for aryl hydrogens. Thus, the alphadeuterium exchange rate in toluene differs from the rate in benzene by a factor of 10^6 in dimethylsulphoxide and only 70 in ammonia and 50 in cyclohexylamine.

Streitwieser et al[337] have studied the stereochemistry of the exchange in optically active ethylbenzene-α-d in cyclohexylamine containing a lithium cyclohexylamide catalyst. Each of the alpha-hydrogen exchange events was found to involve an approximately 82% retention. However, complete racemisation was found in the case of optically active 2-phenylbutane-2-d and caesium cyclohexylamide[317]. Consequently, the exchange mechanism varies with the catalyst used. Streitwieser and Caldwell[317] assumed that a four-centre transition state was formed with lithium cyclohexylamide, but a linear one with caesium cyclohexylamide.

Lithium cyclohexylamide (retention)



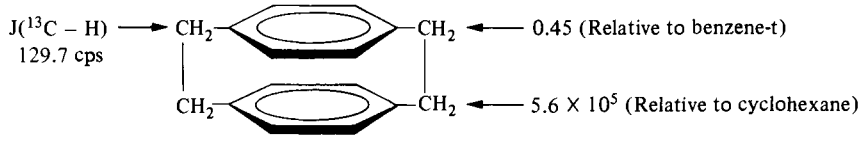
Caesium cyclohexylamide (racemisation)



That the stereochemical pattern alters on going from lithium cyclohexylamide to caesium cyclohexylamide may be explained by assuming that in the organolithium compound, where the distance between the ions in the ion-pair is short, some energy is required for pulling the ions apart so that they could rotate in the ion-pair. With caesium cyclohexylamide, the Cs^+/carbanion electrostatic attraction is sufficiently weak and rotation is possible on the spot.

Streitwieser et al[339] measured secondary isotope effects inherent in the exchange in alpha-deuteriated and ring-deuteriated toluenes. Proto--dedeuteriation of $\alpha,4\text{-}d_2$, $\alpha,2,4,6\text{-}d_4$, and $\alpha,2,3,4,5,6\text{-}d_6$ toluenes studied in the presence of lithium cyclohexylamide at 50°C showed that the rate decrease per deuterium atom in the ring is 2.4% (ortho), 0.4% (meta), and 1.8% (para). The decrease due to the introduction of deuterium was readily explainable since deuterium is an electron donor. However, the isotope effect as a function of the deuterium position has not been explained[339].

The exchange rate measured at 25°C for 2.2 cyclophane XI tritiated in the benzyl position is 0.45 times the rate in benzene-t and 5.6×10^5 times the rate of hydrogen exchange in cyclohexane[340].



(XI)

The fact that 2.2-p-cyclophane XI exchanges faster than does cyclohexane is due to an increase in the C-H bond s-character in the 2.2-p-cyclophane ($J(^{13}C\text{-}H)$ is 129.7 Hz for 2.2-p-cyclophane and 123-124 Hz for cyclohexane). However, this increase is not sufficiently large to account for the factor of 5.6×10^5 found using cyclohexane as the reference compound. Streitwieser assumed that the strongly increased activity of benzyl protons in 2.2-cyclophane is mainly due to conjugation with the benzene ring. He estimated the conjugation effect to be of about 30% of that in toluene.

Polycyclic monoaryl methanes

Streitwieser and Langworthy[341] have determined isotope exchange rates for polycyclic monoaryl methanes in the lithium cyclohexylamide/cyclohexylamine system (Table 42). All the rates are higher than is the toluene exchange rate, owing to additional charge delocalisation caused by condensed aromatic rings[291]. The Hückel molecular orbital approach to these data has been discussed by Streitwieser et al[276]. The technique is exactly the same as that used in the case of equilibrium acidity (Ch. I, Section 6). Two correlation lines were obtained, one for methyls bonded to groups of the phenyl or β-naphthyl type, the other for the alpha-naphthyl compounds whose peri-hydrogens exert a spatial effect on the coplanarity of the anionic methylene group. The first line is shifted by 0.06β from the second one, so that the torsion angle of the exo-cyclic methylene group with respect to the aromatic system is about 17° in carbanions of the alpha-naphthyl type.

TABLE 42

Relative Isotope Exchange Rates for Methylarenes-α-d in Lithium Cyclohexylamide/Cyclohexylamine at 50°C

Ar in $ArCH_2D$	k_{rel}[341]	$pKa(ArCH_3)$[342]
Phenyl	(1.00)	(40.9)
1-Naphthyl	10.3	37.4
2-Naphthyl	7.4	37.9
3-Phenanthryl	14	37.0
9-Phenanthryl	19	36.5
2-Anthracenyl	31	35.8
1-Pyrenyl	190	33.0
2-Pyrenyl	15	36.9
4-Pyrenyl	40	35.4
3-Fluoranthyl	200	33.0
8-Fluoranthyl	14	37.0

Tupitsyn and his coworkers[343] determined the deuterium exchange rate for substituted 1-methylnaphthalenes in a C_2H_5OK/C_2H_5OD system at 180°C. The following rate constants (x 10^5 sec^{-1}) were obtained: H, 1.6; 2-NMe_2, 0.33; 2-OMe, 1.1; 4-F (Cl, Br, CN), higher than 1.6; 4-NO_2, 1710 (at 45°). The substituents effect pattern agrees with their ability to stabilise a negatively charged carbanion site. It is noteworthy that the deuterium exchange rates ratio of 1.5 found for 1-methyl- and 2-methylnaphthalenes in alcohol, corresponds to the $k(\alpha\text{-}CH_3C_{10}H_7)/k(\beta\text{-}CH_3C_{10}H_7)$ of 1.1 found in cyclohexylamine.

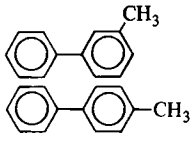
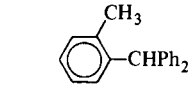
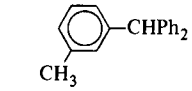
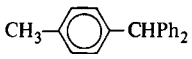
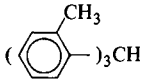
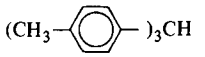
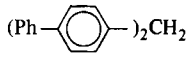
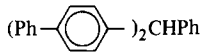
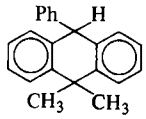
Polyaryl methanes

Hydrogen exchange in triphenylmethane in a lithium cyclohexylamide/cyclohexylamine system is 10^3 times as fast as in toluene[342,344]. This is undoubtedly due to the higher stability of the triphenylmethyl anion caused by conjugation with the phenyls. The electron-donor methyls introduced in the benzene rings decelerate the exchange, with the greatest effect being due to ortho methyl groups[345]. Tri(o-methylphenyl)methane studied in a N-methylaniline/lithium N-methylanilide system did not react in eight days at 150°C (Table 43). The strong effect observed is apparently due to spatial hindrance operating in the process of the formation of the planar configuration. The introduction of a phenyl group in the para-position increases the conjugation in the triphenylmethane molecule and therefore accelerates the exchange rate markedly.

Hydrogen exchange reactions in polyaryl methanes carried out in methanol or in dimethylsulphoxide display a rather low primary isotope effect[331,342]. However, k_D/k_T is 2.90 in a lithium cyclohexylamide/cyclohexylamine system[347], i.e. this isotope effect is fairly high. Streitwieser et al[342] assigned this fact to the internal return mechanism operating in di- and triaryl methanes in methanol. He assumed that k_2 (eq. 2) in methanol at 100°C is the same, whichever of the hydrogen isotopes be exchanged, and found that k_1/k_2 (in

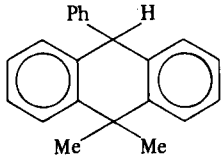
TABLE 43

Relative Rate Constants, Activation Parameters, and KIE Values, for Methane Hydrogen Exchange in Mono-, Di-, and triarylmethanes.

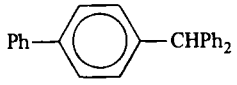
Compound	k_{rel} ($PhCH_3$ = 1). LiCHA[344]	MeOH/MeONa[342] $\Delta H^{\neq}$ kcal/mole	$\Delta S^{\neq}$ e.u.	k_D/k_T (MeOH)[342]	pKa^{CHA} CsCHA[346]	k_{rel} in LiNMA-NMA 150° [345] ($PhCH_3$ = 1)
$PhCH_3$	(1.00)				(40.9)	
	2.2					
	4.6				37.8	
Ph_2CH_2	270	33.80	0.56	1.52 [a]	33.4	0.60
Ph_3CH	960	32.28	0.70	1.34 (2.90 in CHA)	31.4	(1.00)
						0.26
						0.40
						0.41
						no exchange in 182 hrs
					33.0	0.16
	1.3x10^3	30.20	-3.33		30.84	
	2.2x10^3	28.88	-6.14		30.20	
	3.7x10^4	27.80	-4.05	1.64	28.04	

NMA = N-methylaniline
LiNMA = lithium N methylanilide
CHA = cyclohexylamine
CsCHA = caesium cyclohexylamide
k_D/k_T = 1.3 in dimethylsulphoxide/potassium tert-butoxide at 25°C[331]

methanol) measured for the exchange of tritiated hydrocarbons increases over the following series.



0.15



0.21

Ph_2CH_2 0.28

Ph_3CH 0.66

The k_{-1}/k_2 (cyclohexylamine) values found for tritium exchange in cyclohexylamine at 28°C are as follows: triphenylmethane-α-t, 0.02; toluene-α, α-d_2-α-t, 0.06. The internal return mechanism is more important in the case of deuterium exchange.

The data in Table 43 suggest that the following conclusions can be made.

(1) In methanol, k_2 is 1.5 to 7 time k_{-1}, in cyclohexylamine the factor is 50 to 160. This means that the internal return mechanism is much more probable in methanol.

Schriesheim et al[338] assumed that in alcohol alkali salts of CH-acids form tight complexes of the type (R^-K^+) HOR′. To explain the low kinetic isotope effect observed for a dimethylsulphoxide/potassium tert-butoxide system (always containing alcohol admixture) these workers assumed that the decomposition of the complex was the slow step.

$$\left[(R^-K^+)HOR'\right]_{solv} \longrightarrow \left[R^-K^+\right]_{solv.} + HOR'$$

$$\downarrow \text{DMSO}$$

$$RH+K^+ \ ^-CH_2SOCH_3$$

DMSO = dimethylsulphoxide

Consequently, the exchange rate is governed by the stability and the concentration of the complex rather than by the ionisation of the C-H bond. This resolves essentially into the case $k_2 < K_{-1}$, i.e. the internal return mechanism.

(2). In methanol, the probability of the internal return mechanism being involved for a narrow series of polyarylmethanes increases with pKa. This is easily understandable because the inverse reaction rate, k_{-1}, should be high and the situation $k_2 < k_{-1}$ should be very probable. Triphenylmethane, however, distinctly deviates from this regularity, its k_{-1}/k_2 value is very high (see Section 1 of this Chapter).

For the internal return mechanism the rate constant is given by the following relationship;

$$k_{obs} = (k_1/k_{-1})k_2$$

If the steps k_1 and k_{-1} obey the Brönsted principle (Chapter V), then at $\alpha+\beta = 1$ we have,

$$\Delta lg k_1 = -\alpha \cdot \Delta pKa$$

$$\Delta lg k_{-1} = \beta \cdot \Delta pKa$$

whence

$$\Delta lg k_{obs} = - \Delta pKa + \Delta lg k_2$$

Consequently, if k_2 is a constant, the Brönsted plots for the internal return mechanism will have a slope of unity.

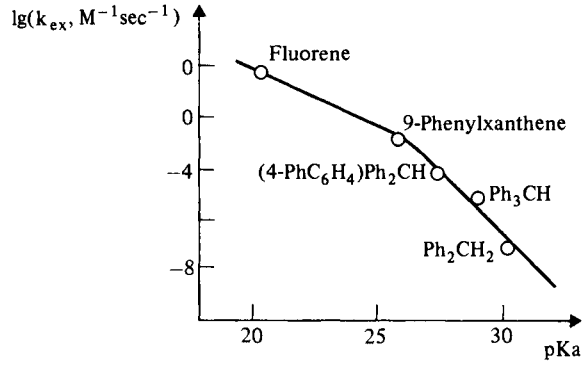


Fig. 10 Experimental Brönsted plot for hydrogen exchange in CH_3OD-$(CD_3)_2SO$ (3:1)/CH_3OK (Data from Ref. 348).

Figure 10 (and Table 44) show logarithmic constants of hydrogen exchange plotted again pKa for some hydrocarbons in a CH_3OD-DMSO-CH_3OK system where CH_3OD/DMSO = 3/1. This plot demonstrates that the slope increases up to $\alpha \sim 1$ at pKa(RH)~26 and the transition from a small slope to a very steep one is very pronounced taking an interval of about 1 pKa unit.

This increase in the Brönsted slope in going from substituted fluorenes (α =0.4) to polyaryl methanes(α=0.6) observed in a CH_3OD/CH_3ONa system by Streitwieser et al[342], may also be due to an increase in the contribution of the internal return mechanism.

Figure 11 reflects the data obtained by Shatenshtein[308] for the exchange of four CH-acids in a KND_2-ND_3 system. Streitwieser's pKa scale is used. The transition from lower α values (indene, fluorene) to the higher α values (triphenyl- and diphenylmethanes) is also evident in this case.

e. Compounds with cyclopentadiene ring

Cyclopentadiene (pKa 15.5) readily exchanges with heavy water in dioxane containing an N,N-dimethyl-α-pyridoneimine catalyst[351]. The isotope equilibrium is reached at 20°C in 20 hours, all the hydrogen atoms

being substituted by deuterium. This easy exchange may be due to the fact that the hydrocarbon is transformed to an aromatic anion in which all the CH groups are identical. The intramolecular mechanism of this exchange is discussed in Chapter IV.

TABLE 44

Rate Constants and Activation Parameters for Isotope Exchange in Some CH-Acids in $CH_3OD/DMSO/CH_3OK$ ($CH_3OD/DMSO$ = 3/1) at 75°[348]

No.	Compound	pKa in DMSO	$lg\,k_{obs}$	$\Delta H^{\neq}$ kcal/mole	$\Delta S^{\neq}$ e.u.
1.	Fluorene	20.5[a)]	-0.30	16.7	-10.8
2.	9-Phenylxanthene	25.5	-2.87	26.9	
3.	4-Biphenylyldiphenyl-methane	27.3	-4.42	28.2	1.8
4.	Triphenylmethane	28.8[b)]	-4.86	29.6	3.9
5.	Diphenylmethane	30.2	-713	33.5	10.7

a) pKa is ca. 27 in methanol as obtained from $k_1 = 4.3\times10^{-4}$ and $k_{-1} = 2\times10^{+5}$ 1/mole sec for the reaction of fluorene with CH_3O^- in methanol[349] and pKa(MeOH) = 18.3 in methanol[345].

b) pKa is ca. 34 in methanol[104]

DMSO = dimethylsulphoxide.

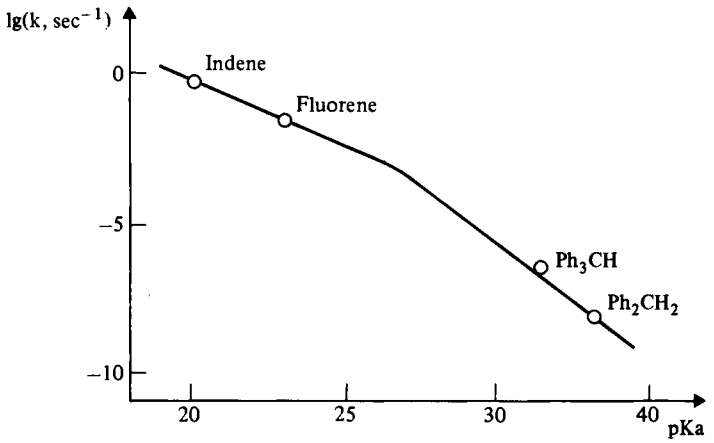


Fig. 11. Experimental Brönsted plot for hydrogen exchange in ND_3/KND_2 (Data from Ref. 308 from Streitwieser scale).

TABLE 45

Rates and Activation Parameters, for Hydrogen Exchange in CH_3ONa/CH_3OH at 45°C[352]

Compound	$10^4 k_{exchange}$ 1/mole sec	$\Delta H^{\neq}$ kcal/mole	$\Delta S^{\neq}$ e.u.	pKa(CHA)[353]
1,2-o-Phenylene-7,12--dihydropleiadene	5630	17.30	-5.99	15.39
9-Phenyl-3,4-Benzofluorene	1030	-	-	15.68
9-Phenylfluorene	173	21.30	0.20	18.49
3,4-Benzofluorene	90.3	20.95	-2.20	19.75
Indene	50.0	20.29	-5.43	19.93
1,2-Benzofluorene	31.9	18.49	-11.98	20.35
4,5-Methylenephenanthrene	6.85	23.66	1.21	22.93
Fluorene	3.95 4.3;[349]	23.26	-1.16	23.04
2,3-Benzofluorene	2.15	-	-	23.47
9-Methylfluorene	1.1;[349]			
9-Ethylfluorene	0.78;[349]			
9-Benzylfluorene	3.1;[349]			
9-Methoxymethylfluorene	56;[349]			
9-Trifluoromethylfluorene	86,000[349]	12.3	-15.6	

CHA = cyclohexylamine

Indene (pKa 19.9 in cyclohexylamine) and fluorene (pKa 23) exchange their methylene hydrogens appreciably more slowly, Table 45 lists Streitwieser's data on derivatives of fluorene and other compounds studied in a CH_3ONa/CH_3OH system[352].

Kinetic isotope effects have been measured for fluorene, 9-phenylfluorene, and 9-phenyl-3,4-benzofluorene. The value of k_D/k_T was about 2.5 (k_H/k_D of about 8) in all cases. This infers a noticeable C-H bond ionisation and, in accordance with what has been said on polyarylmethane acidities, allows the internal return mechanism to be ruled out. Fluorene studied in liquid ammonia[354] and in methylamine[355] gave a k_D/k_T value of 1.9 and 2.4, respectively.

The $\log k_{obs}$ vs pKa dependence observed for fluorenyl compounds (α=0.37) by Streitwieser et al allowed him[352] to assume that charge delocalisation in the transition state is only 37% of the delocalisation in the respective carbanions and, hence, the transition state has a pyramidal structure.

Table 46 lists the data obtained in anhydrous dimethylsulphoxde, which illustrate the effect of base strength upon the proton abstraction rate in fluorene compounds. The pKa of anion catalyst and the $\lg k_1$ (or $\lg k_{-1}$) vary in parallel with each other, but not linearly.

f. Acetylenes

Acetylenes possess rather high equilibrium acidities because the lone-pair s-character is approximately 50% in the anion $RC{\equiv}C^-$. The

terminal acetylene group readily exchanges its proton in polar solvents containing bases[151,358-361]. The acetylene hydrogen exchange rates in a t-BuOH-water-t-BuO^- system (t-BuOH/water is 45/55) may be arranged as follows.

$HOCH_2CH_2C{\equiv}CH$	$k(M^{-1}\ sec^{-1})$: 8.9	$(EtO)_2CHC{\equiv}CH$	$k(M^{-1}\ sec^{-1})$: 96
$HOC(CH_3)_2C{\equiv}CH$	34	$MeOCH_2C{\equiv}CH$	99
$PhC{\equiv}CH$	43		

Probably, the substituent effect observed is due to field and inductive effects, not to resonance[291].

TABLE 46

Hydrogen Exchange Rates for 9-Methylfluorene-9t and Fluorene-9t in Dimethylsulphoxide/anion systems at 25°C

Compound	Anion of (pKa)	k_1, $M^{-1}\ sec^{-1}$	k_{-1} $M^{-1}\ sec^{-1}$	Ref No.
9-Methylfluorene	9-Phenylfluorene (18.5)	0.1	170	286
	Indene (19.9)	20	400	286
	4,5-Methylene-phenanthrene (20.3)	1.4×10^3	200	356
	Fluorene (23)	1.6×10^3	270	286
	$CH_3SOCH_2^-$ (33)	above 10^7	-	286
Fluorene	Fluorene (23)	0.5	0.5	357
	9-Methylfuorene (above 23)	270	1.6×10^3	286

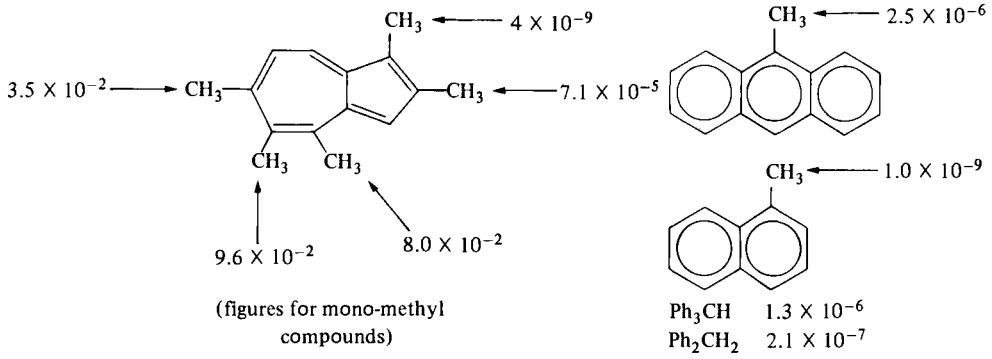
Kresge and Lin[362] studied the interaction of phenylacetylene with aqueous bases. They found that using amine catalysts the reaction rate depends on the base strength (general base catalysis, $\beta = 0{,}97$). No isotope effect was found, so the proton abstraction is not a limiting step. (k_H/k_D was 0.95 with OH^- catalysts and 1.17 with a 1-methylimidazole catalyst)

g. Methylazulenes

Weiss[363 364] studied isotope exchange kinetics for isomeric methylazulenes in deuterated pyrrolidine at 200°C. Listed overleaf are rate constants (sec^{-1}) of hydrogen exchange in methyl groups in various positions of bicyclic systems. Methyl groups in all the positions are more active than they are in 1-methyl naphthalene, the CH_3 hydrogen activity in the seven-membered ring is 10^3 to 10^7 that in the five-membered ring.

2. Halogenated Derivatives

Hydrogen exchange in fluorinated organic compounds has been extensively studied, due to the interesting peculiarities exhibited by these compounds. Thus, fluorine introduced in the alpha-position vis-à-vis a C-H bond subject to the reaction may accelerate, but may also decelerate, the exchange (α-effect). The acceleration, if present, is usually markedly weaker than it is with chlorine or bromine. This does not agree with the high electronegativity of fluorine (4.0 in terms of the Pauling scale).



The trifluoromethyl group significantly enhances hydrogen exchange for the alpha-C-H bond under mild conditions. This fact is often assigned to "negative hyperconjugation" of the CF_3 substituent with the carbanion site, but this assumption is not always necessary. The effect of fluorine upon equilibrium CH-acidity has been discussed in detail in Chapter II. In the present Section, the available quantitative data on isotope exchange rates in fluorinated hydrocarbons is dealt with in detail.

Ridge and Beauchamp[365] have studied proton abstraction rates for fluorolefins in the gas phase. They determined the dehydrofluorination rates of fluorinated ethanes acted upon by CD_3O^- in the gas phase as indicated below; (proton abstraction was the slow step).

				kx10-10 cm3/mole.sec
(a) CH_2FCH_3	+ CD_3O^-	→ $CH_2F\text{-}CH_2^-$	+ CD_3OH	0.44
(b) CHF_2CH_3		→ $CHF_2\text{-}CH_2^-$		3.6
(c) CF_3CH_3		→ $CF_3\text{-}CH_2^-$		7.9
(d) CHF_2CH_2F		→ CHF_2CHF^-		5.6
(e) CF_3CH_2F		→ CF_3CHF^-		3.4
(f) CF_3CF_2H		→ $CF_3CF_2^-$		19.0

These data, as well as those given in Chapter II, show how capricious is the effect of fluorine on the carbanion stability. Fluorine introduced in the beta-position may either raise or diminish the proton abstraction rate (k(c)>k(b)>k(a), but k(e)<k(d)); the same is true with the alpha-substitution (k(d)>k(b), k(f)>k(e) but k(e)<k(c)).

These facts are, probably, best explainable in terms of the opposite effects

exerted by the alpha- and beta-fluorine atoms upon the transition state geometry. If it is assumed that a carbanion site is stabilised by the beta-fluorine atoms through hyperconjugation or pi-induction (see[189] for a review), then these effects should raise the p-character of the carbanion site, in other words, favour the formation of a planar anion. However, the flatter the carbanion the stronger the destabilising effect of the fluorine lone-pair. These oppositely directed effects make it impossible to correlate the exchange rate with the number of either alpha- or beta-fluorine atoms.

Alpha-alkoxy groups show a similar behaviour, and indeed, the same may be true for R_2N groups since nitrogen and carbon lie in the same Period. This is demonstrated by the data obtained by Hine et al[366] who measured deuterium exchange rates for substituted methyl acetates in a CH_3OD/CH_3ONa system (Table 47). The pattern becomes even more striking when the Taft correlation technique is applied: the methyl alpha, alpha-difluoroacetate reactivity turns to be 10^{-12} times that required by the alpha-fluorine σ value. This is due to the fact that the two fluorine atoms do not consent to a planar anion, so no conjugation with the carbonyl group is possible.

TABLE 47

Isotope Exchange Rates in Methyl Esters of Substituted Acetic Acids in CH_3OD/CH_3ONa at 36°[366].

X in XCH_2COCH_3	k_{rel} (CH_3COOCH_3=1)	Effect of α-F or α-CH_3O
H	1[a]	
CH_3	0.13	
C_2H_5	0.10	
C_6H_5	>300	
$PhCH_2$	0.44	
CH_3OCOCH_2	2.84	
CH_3O	0.78	small deceleration
CH_3OCH_2	20.5	
$C_2H_5OCH_2$	6.3	
F	1.82	small acceleration
X in $X_2CHCOOCH_3$	**k_{rel} (CH_3COOCH_3=1)**	**Effect of α,α-F_2 or α,α-$(OMe)_2$**
CH_3O	0.010	steep deceleration
F	0.006	

a) $k = (1.28\pm0.04) \times 10^{-3}$ 1/mole sec.

Streitwieser and Mares[367] who studied hydrogen exchange in alpha-d(t) -benzylidene fluoride (k_D/k_T 2.9) and 9-phenylfluorene-9-d(t) (k_D/k_T 1.9) found that in MeOH/MeONa the exchange rate in 9-fluorofluorene is about 12% of that in the unsubstituted fluorene while in lithium cyclohexylamide/ cyclohexylamine the rate for benzylidene fluoride is 10^4 times that for toluene. In potassium-tert butoxide/tert butanol the exchange in benzal fluoride, is also faster than in toluene[285]. Streitwieser assumed that fluorine stabilises the pyramidal structure of ($C_6H_5CF_2^-$) and destabilises the

planar structure of the fluorenyl anion. The same follows from the equilibrium acidity data (see Chapter II). However, the trifluoromethyl group in position 9 of fluorene increases the exchange rate by a factor of 2×10^4 in a MeONa/MeOD system.[349 350]

TABLE 48

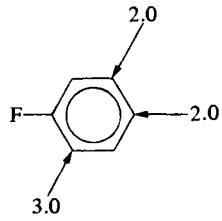
Activation Parameters and Isotope Effects in Hydrogen Exchange Reactions of Fluorinated CH-acids in $CH_3OH(D)/CH_3ONa$

Compound	k_{obs}, 1 mole^{-1} sec^{-1}	$\Delta H^{\neq}$ kcal/mole	$\Delta S^{\neq}$ e.u.	k_H/k_D	Ref. No.
Pentafluorobenzene	1.36×10^{-1} (40°)	18.0	-5.6	1.0	368
1,2,3,4-Tetrafluorobenzene	5.3×10^{-7} (40°)	27.3	-0.3	-	364
1,3-Difluorobenzene-t	5.79×10^{-7} (40°)	27.9	1.9	1.1	368
1,3-Difluorobenzene-d	-	27.3	-4.3	-	369
1-Hydrondecafluoronorbornane	9.3×10^{-2} (-63.5°)	12.4	-3.7	-	370
9-Trifluoromethylfluorene	3.13×10^{-3} (-45.3°)	12.3	-15.6	-	349
$CF_3(CF_2)_6H$	1.39×10^{-5} (70°)	28.1	2.3	2.1	371
$(CF_3)_2CDH$	1.82×10^{-4} (20°)	20.3	-2.8	2.4	371
CF_3H	3.43×10^{-6} (70°)	-	-	2.1	371

Streitwieser et al[368] have postulated the internal return mechanism for isotope exchange in tritiated polyfluorobenzenes in a $CH_3OH(D)/CH_3ONa$ system. The activation parameters are listed in Table 48. Included are also the data for other fluorinated CH-acids. The internal return mechanism assumption is based on the fact that there is no kinetic isotope effect in fluorinated benzenes which is reminiscent of the data obtained in the case of exchange mechanisms in polyaryl methanes in a methanol/dimethylsulphoxide system. The internal return mechanism in polyfluorobenzenes is observed at rather low pKa values (pKa of C_6F_5H is 23, polarographic scale). This may mean that there is no unit Brönsted plot embracing all CH-acids because, if the internal return mechanism operates, the Brönsted coefficient should be equal to unity when k_2 is independent of the hydrocarbon structure.

Quite a different result was obtained by Streitwieser and Mares[372] for fluorobenzene in a lithium cyclohexylamide/cyclohexylamine system. The k_D/k_T values for hydrogen exchange at various positions of the fluorobenzene ring are shown below:

The internal return mechanism evidently does not hold in the case of cyclohexylamine. Probably, the exchange mechanism is strongly dependent on



the solvent used. Kinetic isotope effect values are known to be often close to unity in hydroxyl-containing solvents.

The kinetic isotope effect will be discussed in further detail in the last section of this Chapter.

Unlike fluorine, the other halogens always raise the kinetic acidity of the adjacent C-H bond. Klabunde and Burton[140] showed that in a dimethylsulphoxide/methanol system (50/50 mole/mole) containing triethylamine substituents X in the molecules $(CF_3)_2C(X)H$ may be arranged in the following series by their ability to accelerate hydrogen exchange.

$$CF_3 > Br > Cl > I > Ph > F > OCH_3$$

where the exchange rates of bromine, chlorine, and iodine (not fluorine) are comparable to that of one of the strongest inductive stabilisers of anions, namely the CF_3 group. The results[140] are summarised in Table 49.

TABLE 49

Relative Exchange Rates for Halogenated Derivatives in Dimethylsulphoxide/methanol/triethylamine at 37°C [140]

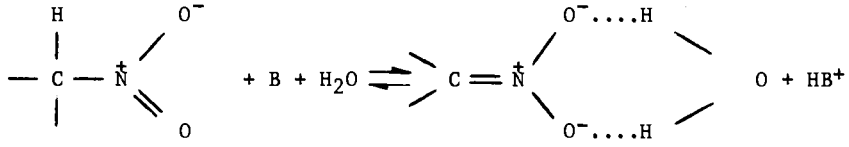
R in $(CF_3)_2C(X)H$	k_{rel}	Compound	k_{rel}
CF_3	very high	CBr_3H	160
Br	2,227	CCI_3H	18.2
CI	651	CF_3CBr_2H	3.03
I	154		
Ph	(1.00)	CF_3CCI_2H	2.33
F	0.86		
OCH_3	very low		

Values of the kinetic isotope effect of bromoform are k_H/k_D 2.3 and k_D/k_T 1.6[140]. Margolin and Long[373] found that for chloroform in aqueous buffers, k_H/k_D is 1.42 (25°C). No general base catalysis has been observed as occurs

in the case of phenylacetylene[362]. The entropy of activation is very positive (+ 15 e.u at 25°C), but decreased on adding dimethylsulphoxide. Margolin and Long[373] assumed that the highly positive $\Delta S^{\neq}$ was mainly due to desolvation of hydroxyl ions in the transition state.

3. Nitro Compounds

Nitroalkanes in aqueous solutions are strong acids comparable with phenols and the proton abstraction rate in these compounds is rather high. This is due to conjugation of the nitro group with the carbanion site; the proton abstraction product is not a carbanion, it is the aci-anion in which the negative charge is almost totally localised on the oxygen atoms and which, in water, is stabilised by hydrogen bonds (cf. Ch. II).



To study the kinetic acidity of nitroalkanes, Eigen and Ilgenfritz[32] used spectrophotometry and other workers have used methods based on base catalysed halogenation kinetics[374-377]. The interest in nitroalkane acidities is mainly due to the fact that "anomalous" Brönsted plots are observed for these compounds, with α being negative or exceeding unity. Also, tunnel proton transfer has been observed in nitroalkanes[374]. Proton abstraction stereochemistry has been studied in the case of nitrocycloalkanes[236]. These problems are all considered in the ensuing sections starting with a discussion of the kinetic acidity of nitrocompounds in water (Table 50).

TABLE 50

Proton transfer Rates, from Nitro Compounds to Water

$$R_2CHNO_2 + H_2O \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2CNO_2^- + H_3O^+$$

Compound	k_1 sec^{-1}	k_{-1} $M^{-1} \times sec^{-1}$
CH_3NO_2	4.3×10^{-8}	680
$CH_3CH_2NO_4$	3.7×10^{-8}	15
$ClCH_2NO_2$	5.7×10^{-7}	50
$BrCH_2NO_2$	1.3×10^{-3}	-
$CH_2(NO_2)_2$	8×10^{-1}	3,100
$CH_2(COOEt)NO_2$	6.3×10^{-3}	4,200
$CH_3COCH_2NO_2$	4×10^{-2}	5.000

The data of Table 50 suggest that the proton abstraction rate as a function of the substituent in nitromethane increases across the following series.

$$CH_3 < H < Cl < Br < COOEt < COCH_3 < NO_2$$

This series is in a better fit with the Hammett σ constants than with the σ*

constants. This probably indicates that the substituents are conjugated with the partial double bond formed in the transition state. However, Bordwell et al[236] who studied ring-substituted $ArCH_2CHMeNO_2$ (13 compounds; ρ 0.665) and ring substituted $ArCHMeNO_2$ (12 compounds; ρ 1.44) believe that conjugation does not contribute significantly, because the exchange rates found for the two series correlate fairly well whereas conjugation with the carbanion site is possible in one of these, impossible in the other one.

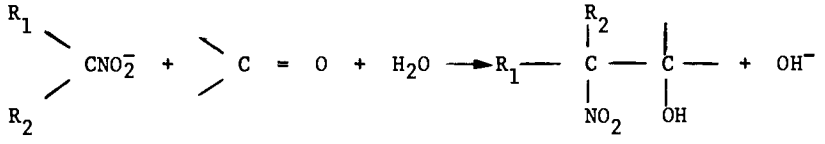
Belikov et al[212] have studied the reaction for another series of nitrocompounds

$$R_2CNO_2^- + H_3O^+ \longrightarrow R_2CHNO_2 + H_2O$$

and obtained the following equation,

$$\lg k_{-1} = 1.6 \sum E_s + 9 \sum \delta^- - 4.0$$

This equation describes the experimental data satisfactorily. It strongly suggests that conjugation favours proton addition to the anion of the nitrocompound (ρ is 9). This is not quite clear because a plausible assumption is that the farther the charge is from the reaction site the less facile will be the reaction affecting this site. Belikov et al[378] reported that anions of substituted nitroalkanes behaved anomalously in their addition across the carbonyl group as well.



The reaction rate increases when R_1 and/or R_2 are (-M)substituents (NO_2, COR, etc.).

4. Carbonyl Compounds

The anomalous effects discussed above for nitroalkane anions are not observed in the case of carbonyl compounds. In Table 51 are listed data obtained in aqueous media. With substituted acetones, the effect of the substituent (k_{-1}) upon the reaction rate of the enolate ions with H_3O^+ may be presented as follows.

$$CF_3CO < NO_2 < COCH_3 < COOEt < Cl < H$$

The series is quite the opposite of the one observed with nitroalkanes (Table 50);

$$CH_3 < H < Cl < Br < COOEt < COCH_3 < NO_2$$

Belikov et al[378] have stated that nitrocompounds behave "normally" when water is replaced by dimethylsulphoxide[378].

Hydrogen isotope exchange has been studied for ketones[379-381] in methanol or in aqueous dioxan and the highest rate was observed for acetophenone whose enolate anion is stabilised by the phenyl group. The exchange of methyl groups in methyl cycloalkyl ketones is ten to twenty times faster than it is in the case of cycloalkyl compounds. The exchange is very slow with the

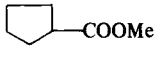
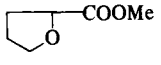
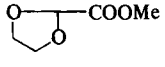
cyclopropyl hydrogen atoms in methyl cyclopropyl ketone. Table 52 compares deuterium exchange in position 2 of propane containing electronegative groups with the exchange in the respective cyclopropyl system[381]. Cyclopropane hydrogen atoms are more active in ketones whilst open-chain hydrogen atoms are more active in the compounds containing CN, CF_3, and $PhSO_2$ groups. The kinetic isotope effect in cyclopropane compounds is not so high that it can be assumed with certainty that proton transfer is the limiting step. Winer et al[381] assume that the anions formed are strongly associated with alcohol molecules and that the limiting step is solvent exchange in the anion/methanol ion-pair (the step k_2, eq. 2).

TABLE 51

Proton Transfer Rates, from Carbonyl Compounds to Water (k_1), and from Hydroxonium Ion to the Respective Enolate Anions (k_{-1})

Compound	k_1 sec^{-1}	k_{-1} M^{-1} sec^{-1}	Ref No.
CH_3COCH_3	$ca.10^{-10}$	$5x10^{10}$	16
CH_3COCH_2Cl	$5.5x10^{-8}$	$ca.1.7x10^{9}$	87
CH_3COCH_2COOEt	$1.2x10^{-3}$	$5.8x10^{7}$	16
$CH_3COCH_2COCH_3$	$1.2x10^{-2}$	$1.2x10^{7}$	16
$CH_3COCH_2NO_2$	$4x10^{-2}$	$5x10^{3}$	87
$CH_3COCH_2COCF_3$	$8.3x10^{-3}$	$5.5x10^{4}$	87

In their extensive studies of the alpha-effect, Hine and Dalsin[383] measured hydrogen exchange rates in substituted methyl carboxylates. The rate constants (x 10^6 M^{-1} sec^{-1}) found in a CH_3ONa/CH_3OH system at 35°C are as follows.

$Me_2CHCOOMe$	9.95		24.9
$Et_2CHCOOMe$	1.95		67.3
MeOCH(Et)COOMe	18.6		5.32
$(MeO)_2CHCOOMe$	10.6		

The points corresponding to the oxygen-containing substituents deviate from the plot of lgk_{obs} vs. the sum of the Taft σ^* constants, cf. Section 2 of this Chapter.

TABLE 52

Substituent Effect upon Relative Hydrogen Exchange Rate in Isopropyl and Cyclopropyl Groups, in Methanol/sodium methoxide at 53°C[381]

Compound	k_{rel}	k_D/k_T	Compound	k_{rel}	k_D/k_T	k_{iso}/k_{cyclo}
	1,330	-		(1.00)	1.6	1,330

TABLE 52 *continued*

Compound	k_{rel}	k_D/k_T	Compound	k_{rel}	k_D/k_T	k_{iso}/k_{cyclo}
	1,550	2.0		1.8	-	850
	4,000	2.0[a)]		2.4	1.8	170
	4.4	2.34		0.42	1.7	10
	-	2.3		5,500	1.5	-
	0.81	1.13		11.8	1.35	0.067
	10^{-7}	-		$2x10^{-3}$	-	$5x10^{-3}$
	1.63	-		55.0	-	0.029

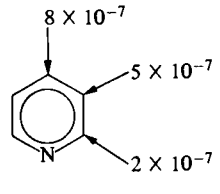
a) k_H/k_D is 5 to 9 in liquid ammonia containing calciumintrate[382]

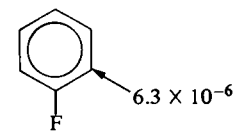
5. Heterocyclic compounds

Much work has been carried out on hydrogen isotope exchange in heterocyclics. This deals with the various problems discussed above and also, with the problem of labelling biologically important molecules such as 5-fluorouracil[384].

a. Six-membered nitrogen-containing heterocyclics

Pyridine enters into hydrogen isotope exchange reactions much more readily than does benzene. This has been demonstrated by Tupitsyn et al[385] who measured the hydrogen exchange rates in a C_2H_5OD/C_2H_5OK system at 140°C and obtained the following values (sec^{-1}).





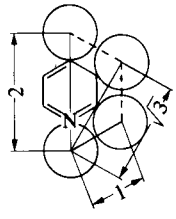
The data on the reactivity of fluorobenzene permits an approximate estimate to be made of the hydrogen exchange rate constant for benzene under these conditions. Shatenshtein[308] showed that the exchange rates observed in an NH_3/NH_2^- system for the ortho-position of substituted benzenes correlate with the σ_I constants of the substituents (ρ_I was 11). The constant ρ_I for ortho-subtituted benzene is as high in other media[385]. Thus, ρ_I is 9.7 in dimethylsulphoxide/potassium tert-butoxide[385]. If it is assumed that ρ is approximately 10 in EtOD/EtOK and σ_I (ortho-f) is approximately 0.5[308], then, the benzene deuterium exchange rate ($k(C_6H_6)$) will be about 10^{-10} sec^{-1}. Even if ρ_I is equal to 5, $k(C_6H_6)$ will be about $10^{-7.5}$ sec^{-1}, an order of magnitude lower than in the pyridine gamma-position.

The higher reactivity of pyridine is readily explainable by assuming that the electronegative nitrogen lowers the electron density on the pyridine carbons and, therefore, stabilises the carbanion and mobilises the protons.

Hydrogen exchange reactivity as a function of the position of the hydrogen atom in the pyridine nucleus increases over the series 2<3<4, in other words, it is higher the farther the proton is from the nitrogen atom. Rate constant ratios obtained for positions 2, 3, and 4 under various conditions are listed below[385-390]. Except for the $NaND_2/ND_3$ system, the reactivities in the different positions do not differ much.

1:2,5:4 (EtOK-EtOD, 140°C[385 386])
1:2,5:3,7 (MeONa-MeOD, 140°C[387])
1: - : 3 (pyrrolidine, 200°C[388])
1:2,3:3 (NaOD-D_2O, 220°C[389])
$1:10^2:10^3$ ($NaND_2$-ND_3, 25°C[390])

The higher reactivity of the C-H bond farthest from the nitrogen may be assigned to a field effect. The nitrogen n-orbital coplanar with the sp^2 orbital of the pyridine carbanion should destabilise the carbanion and its effect will decrease with an increase in the distance between the nitrogen orbital and the C-H bond under ionisation. This may be, very approximately written as follows: $r_2/r_3/r_4 = 1/\sqrt{3}/2$.



(The molecule C_5H_5N is assumed to be a regular hexagon)

Figure 12 shows the logarithmic relative exchange rates in various positions in the nucleus, as a function of 1/r. The obvious linearity supports the assumption that the inductive field effect plays an important role.

For obvious reasons, in acid media (deuterium chloride/deuterium oxide) the reactivities in positions 2, 3, and 4 on the pyridine nucleus change in

the reverse order to that in which they change in basic media[389].

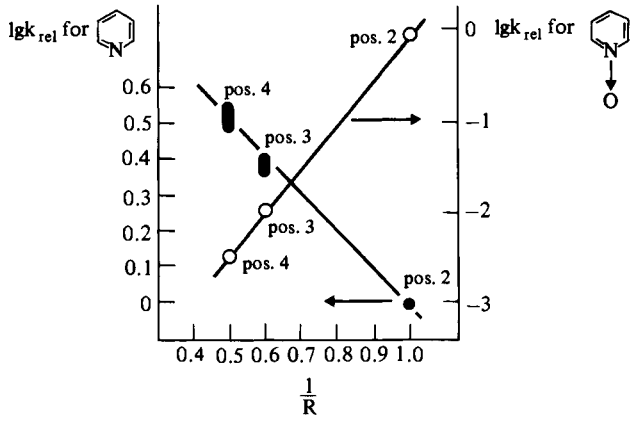
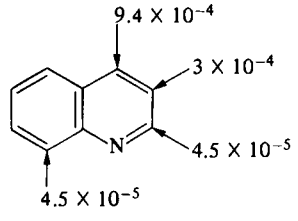


Fig. 12. lgk_{rel} vs. $\frac{1}{R}$ for exchange of hydrogen in positions 2, 3, and 4 of pyridine (the left y-axis) and pyridine N-oxide the right y-axis). R is the distance between ring nitrogen and the respective ring carbon.

Quinoline in its hydrogen exchange reactions is more active than is pyridine[386]. The reactivity of the different positions in the nucleus increases, like in pyridine, over the series 2<3<4. The reactivities of positions 2 and 8 are very close to each other. The scheme below shows k_{obs} values (M^{-1} sec^{-1}) obtained in a CH_3OD/CH_3ONa system at 190°C[397].

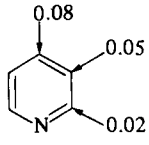


Exchange rates in other condensed six-membered nitrogen-containing heterocyclics tend to increase with the number of nitrogen atoms in the ring. The highest reactivity is observed when the C-H bonds are positioned in a nitrogen-containing ring and lie at the farthest point from the nitrogen atom. This is illustrated overleaf.

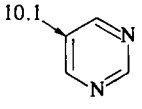
Nitrogen is positively charged in pyridine N-oxide and in N-alkylpyridinium halides, so the hydrogen exchange pattern is the reverse of that observed in pyridine; the rate is at its highest in position 2, and at its lowest in position 4[387,391-395]. This is exemplified by the relative exchange rates reproduced overleaf.

Exchange rates in condensed six membered nitrogen containing heterocyclics.

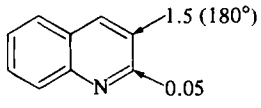
1. Exchange in MeOK/MeOD at 140–160°[386]
($k \times 10^5$ sec^{-1})



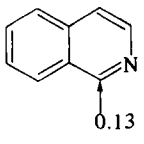
pyridine



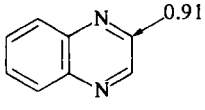
pyrimidine



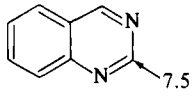
quinoline



isoquinoline

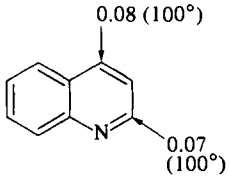


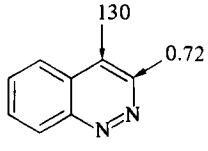
quinoxaline



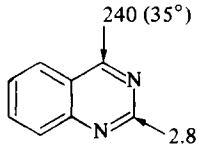
quinazoline

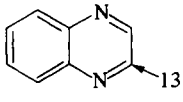
2. Exchange in pyrrolidine-d at 200°[388]
($k \times 10^5$ sec^{-1})

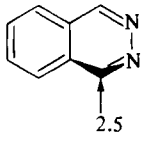




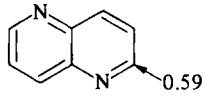
cinnoline



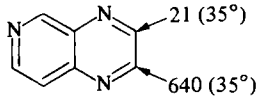




phthalazine

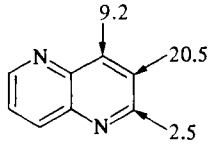


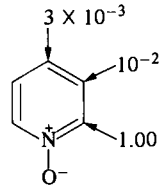
1,5-Naphthiridine



Pyrido [b, c] pyrimidine

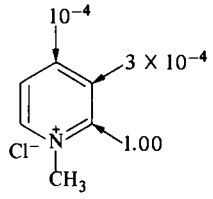
3. Exchange in MeONa/MeOD at 190°[397]
($k \times 10^4$ M^{-1} sec^{-1})





(MeONa–MeOD, 140°[387])

Pyridine N-oxide



($D_2PO_4^-$ –DPO_4^{2-} buffer, 165°[395])

N-alkyl pyridinium halide

In pyridine N-oxide, the pattern of the reactivity versus the position of the proton can be easily explained in terms of the field effect (see plot in Fig. 12).

Pyridine N-oxide and N-alkylpyridinium halides are much more reactive in their hydrogen exchange reactions than is unsubstituted pyridine. This is due to a higher electron-withdrawing activity of the charged nitrogen atom.

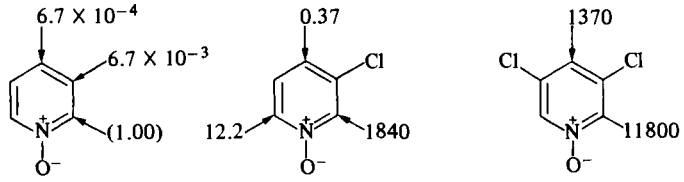
The exchange in the N-methylpyridinium methyl group is also markedly faster than in methane; it is, however, significantly slower than the exchange in the ring[393]. A substituent introduced in position 3 or 4 of the ring of N-methylpyridinium iodide does not seriously affect the methyl reactivity while the effect observed is transduced via the inductive mechanism[396].

In contrast, the substituent effect in the pyridine ring is rather significant. A fluorine or nitro- substituent introduced in position 3 in the ring exerts a steeply accelerating effect and the exchange may occur even in water containing either no catalyst or an amine catalyst. The reactivities in 3-bromo- and 3-nitro-pyridine N-oxides may be arranged as follows, 2>6>4>5[392] which agrees with the assumption of the co-operative field and classical inductive effect of the substituent and the N-oxide group.

The scheme below shows relative deuterium exchange rates measured for pyridine N-oxide, 3-chloro-. and 3,5-dichloropyridine N-oxide in methanol containing sodium methoxide catalyst[394]. The tremendous effect exerted by electron withdrawing substituents in the position 3 and 5 is clearly evident.

Quinoline N-oxide resembles pyridine N-oxide in that the exchange rates should increase over the series 4<3<2; no experimental verification of this point has however, been made so far.

Exchange rates have been studied in various N-oxides and these show that[398 400] the reactivities may be arranged as follows.

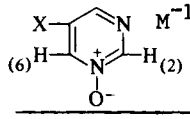
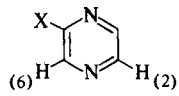


Pyridine-4-d N-oxide < Pyridine-3-d N-oxide < Isoquinoline-3-d N-oxide < Pyridine-2-d N-oxide < Quinoline-2-d N-oxide < Isoquinoline-1-d N-oxide < Quinoxaline-2-d N, N'-dioxide < Pyrazine-2-d N, N'-dioxide < Quinazoline N,N'dioxide.

It can be concluded that the ability of labelled N-oxides to enter into isotope exchange depends, on the whole, on the following factors: (i) the distance between the labelled atoms and the N-oxide group, (ii) the number of hetero atoms, (iii) the presence of condensed benzene ring.

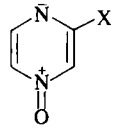
TABLE 53

Substituent Effect Upon Exchange Rate in 5-substituted Pyrimidine N-oxide and Pyrazine N-oxide, NaOD/D_2O[401,402]

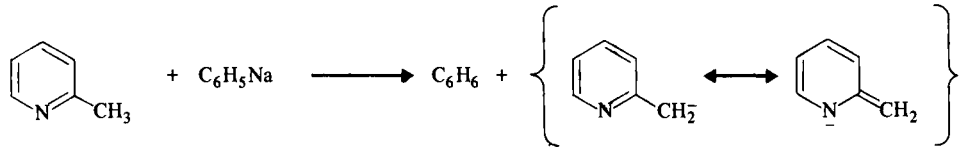
X in 	k(H-2) $M^{-1}min^{-1}$	k(H-6) $M^{-1}min^{-1}$	X in 	k(H-2) $M^{-1}min^{-1}$	k(H-6) $M^{-1}min^{-1}$
$(CH_3)_2N$	slow	0.17	cyclo-$-C_5H_{10}N$	$7.1x10^{-4}$	0.64
CH_3O	$3.1x10^{-3}$	4.7	NH_2	$1.1-10^{-3}$	0.23
CH_3	$1.7x10^{-2}$	$9.8x10^{-2}$	$(CH_3)_2N$	$4.5x10^{-4}$	$3.3x10^{-2}$
H	$1.8x10^{-3}$	$4.7x10^{-2}$	OCH_3	$2.1x10^{-2}$	4.3
Br	slow	540	CH_3	$5.8x10^{-2}$	$4.6x10^{-2}$
			H	0.16	0.16
			CI	0.99	75
			CN	-	280

The substituent effect in position 5 of pyrimidine[401] and pyrazine[402] N-oxides operates via the inductive mechanism. In the case of pyrazine, this would seem to indicate the absence of the following type of structure with a negatively charged nitrogen[402], (see overleaf).

Quantitative data on substituent effects in 5-substituted pyrimidine and pyrazine N-oxide are summarised in Table 53. In both cases the exchange is faster in position 6 whether the donor or the acceptor substituents are present in the ring.



2- and 4-Picolines when acted upon by sodium amide or lithium amide are known to give metalated derivatives whose anions are stabilised by conjugation.



The 3-methyl group does not interact with the ring in the same way. Consequently, an increased reactivity may be expected for the methyl groups of alpha- and gamma-picolines or similar compounds in their base-catalysed hydrogen exchange reactions.

The methyl hydrogen exchange in 2,6-collidine is as fast as is the exchange in p-nitrotoluene whose carbanion is stabilised by one of the strongest (-M) substituents, namely, the nitro group[403]. The methyl hydrogen exchange in 2- or 4-quinaldines is several orders faster than is the exchange in 1- or 2-methylnaphthalenes[404]. Table 54 shows the effect of structure upon hydrogen exchange rate in side chains of the heterocyclics[405 406]. Close examination of these results shows that the following relationships exist:

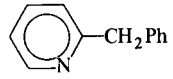
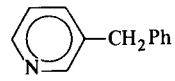
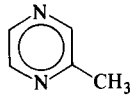
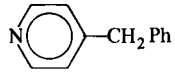
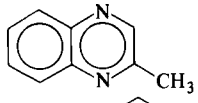
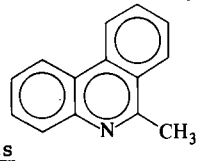
(i) The methylenic hydrogen exchange in benzyl pyridines is faster than is the methyl hydrogen exchange in picolines; (ii) the exchange rate increases with the number of condensed rings (2-picoline < 2-quinaldine < 9-phenanthridine); (iii) diazines react more actively than do monoazines (methylpyrazine > 2-methylpyridine and 2-methylquinoxaline > 2-quinaldine), factor (iii) being more important than (ii); (iv) methyl- and benzylpyridine N-oxides are much more reactive than are the unoxidised compounds.

All these observations may be explained in terms of the inductive field effect concept. No conjugation of the type shown by 2-picoline (see previous formula) is possible in the N-oxides, so the increase in the deuterium exchange rate observed for the side chains is due exclusively to inductive stabilisation caused by a positive charge built up on the nitrogen atom. This agrees with the fact that the difference between the picoline and picoline N-oxide reactivities decreases in going from the alpha- to the beta- and, further, to the gamma- derivatives (Table 54).

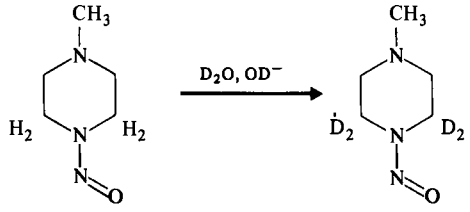
picoline	α	β	γ
Δlgk (oxide minus picoline)	4.74	3.75	2.46

TABLE 54

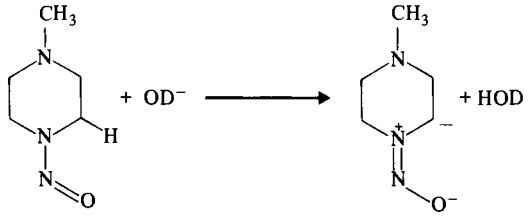
Hydrogen Exchange Rates in Methyl Groups of Six-membered Nitrogen-containing Heterocyclics, $CH_3/OK/CH_3OD$, 25°, [405] [406]

Compound		$-\lg k_{25°C}$	Compound	$kx10^5$ sec^{-1}
Pyridines			Polyaryl methanes	
	2-methyl	8.24		
	3-methyl	10.97	Ph_2CH_2	0.14 (90°)
	4-methyl	6.26		
Quinolines				2.2 (35°)
	2-methyl	5.43		
	4-methyl	5.12		
	6-methyl	11.10		0.7 (50°)
				0.3 (0°)
		5.05		3.6 (35°)
		2.74	Ph_3CH	0.97(90°)
			Fluorene	70
		5.11	N-Oxides of	
			2-methylpyridine	3.50
			3-methylpyridine	7.22
			4-methylpyridine	3.80
			2-benzylpyridine	12.0 (0°)
			3-benzylpyridine	0.33 (0°)
			4-benzylpyridine	16.0 (-10°)
Naphthalenes				
	1-methyl	12.4		
	2-methyl	12.3		
Toluene		13.0		

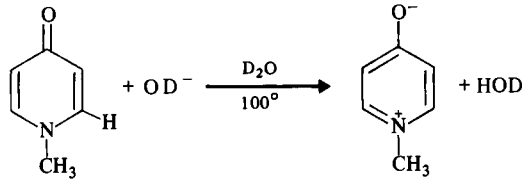
The nitrogen charge effect explains also the facile deuterium for hydrogen substitution which has been observed at positions 2 and 6 in 1-nitroso-4-methylpiperazine and for both CH_3 groups of dimethylnitrosoamine [407].



The carbanion stabilisation is in this case due to the formation of the bipolar form of nitrosoamino group[407].

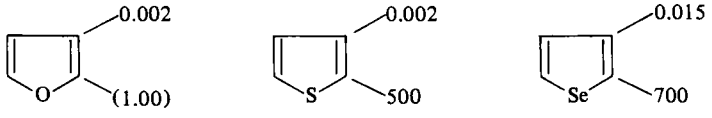


A similar explanation holds for the easy exchange observed at positions 2 and 6 in N-methyl-4-pyridone[408,409], position 2 in 1-methyl-4-pyrimidone, and for related systems.



b. Five-membered heterocyclics

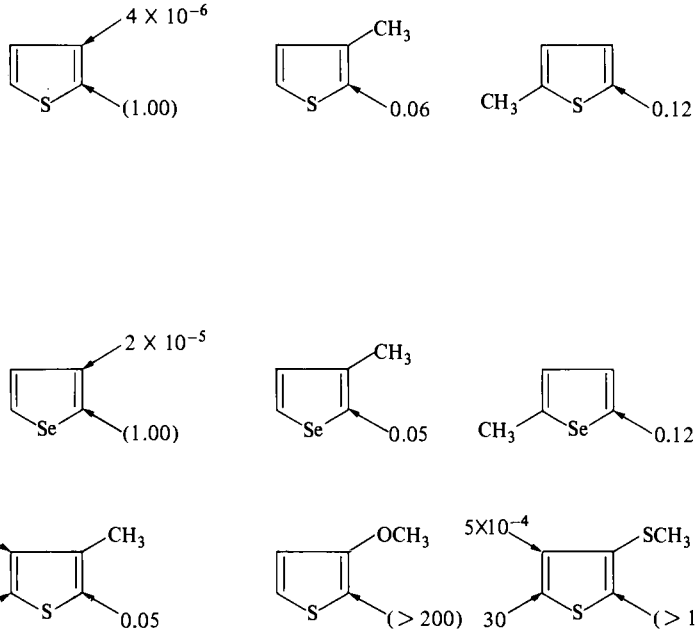
Shatenshtein et al[410-413] studied isotope exchange in deuterated furan, thiophene, and selenophene in a dimethylsulphoxide/potassium tert-butoxide system. The exchange rate increases along the series furan < thiophene < selenophene, the exchange is faster in the alpha-position in all cases.



The alpha-reactivity pattern shown may be assigned to the co-operative d-orbital and alpha-effects.

The alpha-effect (O>S>Se) destabilises the carbanions site whereas the d-orbital effect (Se>S, none with oxygen) stabilises the partial negative charge built up in the transition state (cf. Ch II, Section 4). Negative inductive effects (O>S>Se) evidently play a minor part. The isotope effects for the exchange in the alpha-position are small (furan, k_D/k_T 1.5; thiophene k_D/k_T 1.3, i.e., k_H/k_D is 1.8 to 2.5 eq., 4), so the transition state cannot be assumed to have a pronounced carbanionic character.

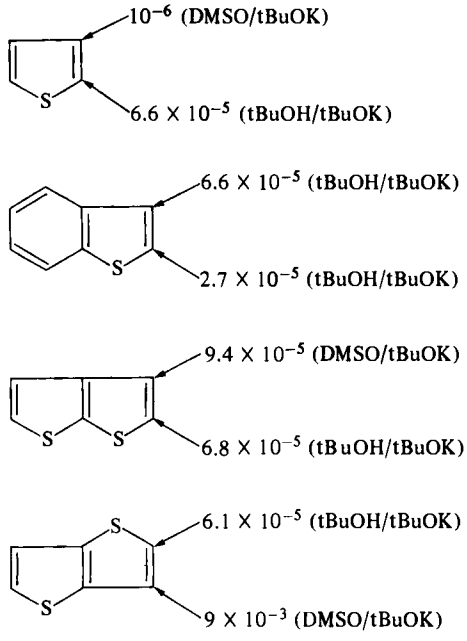
Methyl groups introduced in the furan, thiophene, or selenophene rings hinder the occurence of the following exchange[413] while methoxy and thiomethoxy (CH_3S) substituents in thiophene favour it[411,412].



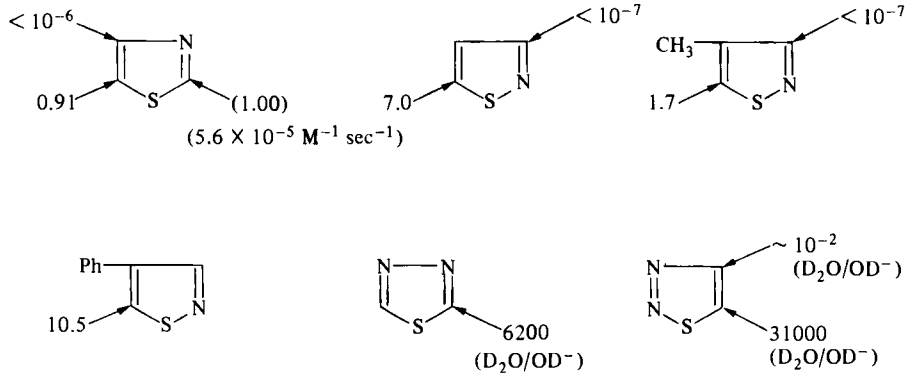
Benzothiophene in a CH_3ONa/CH_3OH system at 160°C exchanges its hydrogen in the 2 position 100 times faster[414] than does thiophene.

Shatenshtein et al[415] have studied deuterium exchange in benzothiophene and isomeric thenothiophenes in dimethylsulphoxide/potassium tert-butoxide, dimethylsulphoxide/lithium tert-butoxide or tert butanol potassium tert-butoxide systems and found the following pseudo-first order constants,

k_{obs} (sec^{-1}).

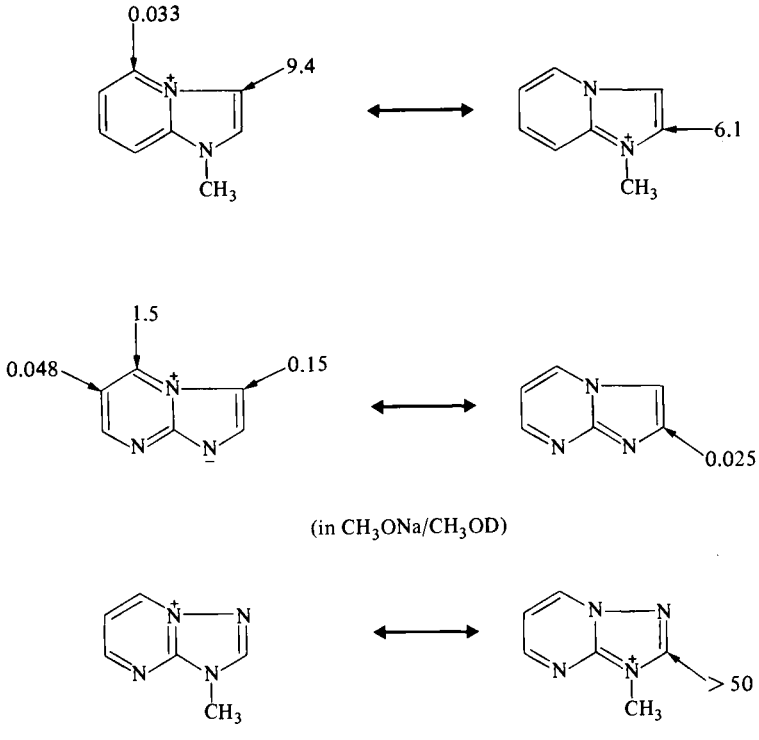


Hydrogen exchange in oxazols and thiazols occurs faster[416,417] than it does with thiophene and even faster in the case of thiadiazols[417]. This is due to an increase in the number of electronegative heteroatoms in the ring. The relative rates measured at 31°C in a CH_3ONa/CH_3OD system[417] are listed below.

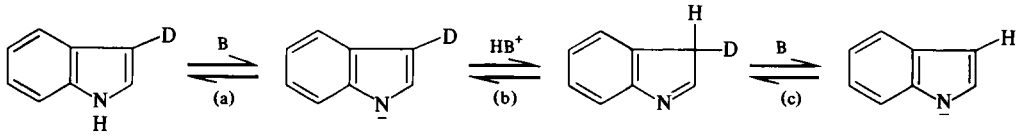


The exchange is very fast in position 2 of N-alkylthiazolium, -oxazolium, and thidiazolium salts[416,418,419], and in N-alkylthiazolium cations it occurs in deuterium oxide at 20° even in the absence of a base[418]. This effect is due to an inductive stabilisation of the transition state which is probably carbanionic caused by the nitrogen charge. The stabilisation is in a similar manner to the case of pyridinium N-oxide and pyridinium salts as discussed in the preceding Section.

A similar positive charge effect has been observed in polyazaindenes[420]. The k_{obs} values (x10^3 M^{-1} sec^{-1}) found in a D_2O/NaOD system at 35°C are listed below.



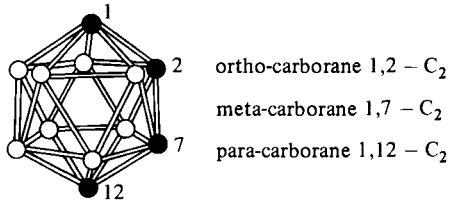
For the unsubstituted indole, an exchange mechanism involving an indolenine intermediate has been proposed[421,422].



The limiting step is either indolenine formation (route b, an S_E2 reaction) or deuteron abstraction from the indolenine (route c). This agrees with a rather high kinetic isotope effect (k_D/k_T is 2 in an aqueous sodium hydroxide system at 25°C.)

6. Carboranes

Carboranes are quasi-aromatic electron-deficient structures whose carbon atoms are in an unusual valence state: each of them being bonded to six other atoms. There are three isomeric carboranes, ortho- meta and para- $C_2H_2B_{10}H_{10}$.



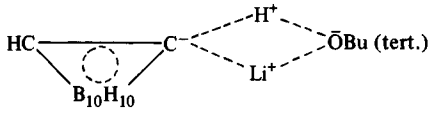
These compounds are CH-acids not BH-acids. The ortho-carborane acidity is comparable to that of phenylacetylene and the para-carborane acidity comparable to that of triphenylmethane (cf. Ch. I).

Deuterium and tritium exchange kinetics in the compounds in various solvents has been studied by Shatenshtein et al[76,77,423-425]. The deuterium exchange rates measured in liquid ammonia are as follows:

	temp., °C	k_{obs} (sec^{-1})
ortho-Carborane	25	6×10^{-2}
meta-Carborane	25	3.1×10^{-6}
para-Carborane	50	8.5×10^{-7}
Fluorene	25	$1\text{-}6 \times 10^{-4}$

Consequently, the proton activity in carboranes decreases over the series ortho > meta > para. The exchange activation parameters depend on the solvent employed. The $\Delta H^{\neq}$(kcal/mole) and $\Delta S^{\neq}$(e.u.) values for ortho-carborane are 6.2 and -4.2 and for the meta-compound these values are 3.0 and -57 in liquid ammonia. In sodium methoxide/ethanol system they are 15.9 and +8 and 26.4 and -10 respectively. The increase in the entropy of activation may be due to desolvation of sodium ethoxide in the transition state. The entropy of activation depends on the counter-ion of the base catalyst it is

-36 e.u. for metacarborane in a tert-butanol/lithium tert-butoxide system. Although this value is less negative than that observed in liquid ammonia, it differs markedly from the $\Delta S^{\neq}$ found in a sodium ethoxide/ethanol system. Probably, a rigid closed transition structire operates in the case of lithium alkoxides.



No kinetic isotope effect has been observed for ortho- and para-carboranes, whatever the solvent (k_D/k_T was of about unity). This means that the base-induced proton abstraction is not the only rate-determining step in the reaction. The hydrogen exchange rate in carborane analogues decreases across the series m-carborane> m-carbaarsaborane > m-carbaphosphaborane[426]. This series agrees with the electron deficiency pattern of these quasi--aromatic systems.

7. Complexes of Transition Metals

Base-catalysed proton abstraction rates in transision metal pi-complexes have been studied by Kursanov et al[427,431] and by Bykova et al [428-430]. The relative exchange rate constant found in potassium tert-butoxide /tert butanol/diethylene glycol (1/1) at 25°C are listed in Table 55.

TABLE 55

Relative Hydrogen Exchange Rates for Transition Metal Cyclopentadienyls in t-BuOK/t-BuOH/diethyleneglycol at 25°C

Compound	k_{rel} (Ph_3CH = 1)	k_D/k_T
Ferrocene	$8x10^{-6}$	-
Cyclopentadienylmanganese tricarbonyl	0.4	-
Diphenylmethane	0.8	1.6
Triphenylmethane	(1.00)	1.7
Nickelocene	40	2.1

t-BuOK = potassium tert-butoxide
t-BuOH = tert-butanol

pi-Cyclopentadienyl manganese and nickel complexes are quite acidic whilst ferrocene is almost incapable of exchanging its hydrogen atoms in basic media. This means that, in contrast with ferrocene, the cyclopentadienyl ligands of nickelocene or cyclopentadienylmanganese tricarbonyl are deprived of the main part of their negative charge.

The kinetic isotope effect for hydrogen exchange in nickelocene is sufficiently high (k_H/k_D is 5.3) to infer that C-H bond ionisation is the rate-controlling step. Hydrogen exchange in bis-pi-benzenechromium, bis-pi-toluenechromiun, and bis-pi-ethylbenzenechromium has been studied in an EtOD/EtONa system[431]. The rates observed were much higher than those found for the uncomplexed arenes. This may be assigned to partial charge transfer from the arene ligand to the metal.

III. KINETIC ISOTOPE EFFECT AND EXCHANGE MECHANISM

The kinetic isotope effect is a criterion for assigning a transition state. Westheimer[432] and Bigeleisen[433] have calculated that the isotope effect should be maximal when the hydrogen in the transition state is bonded symmetrically with the atoms directly participating in the proton transfer. This assumption holds when proton transfer goes in a linear transition state $R^-...H^+....B$.

According to this model the kinetic isotope effect should decrease[437,438] on changing the symmetry of the transition state, whether the transition state structure is similar with the starting pair RH + B or with the resulting pair R^- + HB^+.

Kresge[439] has, for instance, studied the degradation rates of benzenonium ions[439], and found that k_H and k_D (in aqueous perchloric acid; pKa ca. -11) infer an isotope effect maximum corresponding to protonated anisole ($pKa(CH_3OC_6H_5^+)$ -15.3 a compound whose ΔpKa value (equal to pKa ($CH_3OC_6H_5$-pKa(HClO4) is close to zero (Table 56.)

TABLE 56

Kinetic Isotope Effect Versus Benzenonium Ion Structure[439].

Ar in ArH_2^+	Position	pKa (Table 21)	$k_{rel}(C_6H_7^+ = 1)$	k_H/k_D
C_6H_5	-	-23.0	1	3.4
$CH_3C_6H_4$	3	-	6	3.4
	2	-	$4x10^2$	4.6
	4	-	$4x10^2$	5.5
$CH_3OC_6H_4$	2	-	$2x10^4$	7.2
	4	-15.3	$6x10^4$	6.7
$1,3,5-(CH_3O)_3C_6H_2$	2	-4.8	$1x10^{10}$	6.7
Azulene	1	-1.7	$3x10^{11}$	5.6

In his reviews[434-436,440] Bell et al have summarised a considerable bulk of evidence of the kinetic isotope effect observed for the ionisation of carbonyl and nitro compounds in aqueous media. A maximum at about ΔpKa = 0 was observed on the $lg(k_H/k_D)$vs. pKa curve. The ΔpKa variable was the pKa difference between a C-H acid and the acid conjugate with respect to the base;

the bases were carboxylate ions, amines, water, hydroxyl ions, etc. It is evident that at ΔpKa = 0 the transition state structure is close to symmetrical and indeed is absolutely symmetric when a proton is transferred from the acid to the conjugate base of the acid.

The kinetic isotope effect may be varied by varying not only the nature of the base but also the basicity of the medium by, for example, adding dimethyl sulphoxide to protic solvents. This was mentioned for the first time by Saunders et al[441] and by Jones[438] and the experimental verification of this has been obtained by Cockerill[442] for olefin eliminations and by Bell et al[443] for menthone inversion in alkaline media.

TABLE 57

Kinetic Isotope Effect Versus % Dimethylsulphoxide in a Dimethylsulphoxide/tert-butanol-potassium tert-butoxide Mixture for Hydrogen Exchange in Ph_2CH_2 at 25°C

DMSO (mole%)	0	35	57.5	59	89	99.3	100
k_D/k_T	1.8	2.0	2.1	2.0[a]	1.8[a]	1.2[a]	1.3[a]
$H_- - \lg \frac{[tBuO^-]}{[tBuOH]}$ [79][b]	21	21.3	22.3	22.4	24.5	27.4	above 29

a) with t-BuOLi as base.

b) Calculated from the plot of Fig.4-6[104]

DMSO = dimethyl sulphoxide.

Recently Shatenshtein[444] who studied hydrogen exchange in diphenylmethane in a dimethylsulphoxide/tert-butanol/potassium tert-butoxide system showed that the isotope effect is at its maximal at 57.5% (mole/mole) of dimethylsulphoxide (Table 57).

Diphenylmethane in pure dimethylsulphoxide has a pKa of 30 (see Chapter I), so the maximal kinetic isotope effect is in this case observed at a ΔpKa value of about eight rather than zero.

Shatenshtein et al[444] have studied a number of the similar examples and believe that the shift of the maximum is due to an effect of the medium upon the mechanism.

It is also probable that the observed effect may be assigned to the difference between the nature of the Ph_2CH^- and $t\text{-}BuO^-$ groups (the former is less active in its hydrogen bonding with tert-butanol than the latter anion is with Ph_2CH_2) making the transition state symmetric at ΔpKa ≠ 0.

In Table 58 are listed k_D/k_T values obtained for CH-acids discussed in the preceding section of this Chapter. In Fig. 13 is shown the dependence of the kinetic isotope effect (k_D/k_T) on the nature of the CH-acid for a lithium cyclohexylamide/cyclohexylamine system. Concerning Figure 13, the required pKa values have not been measured (except for toluene and benzene, (pKa's 41

and 43 in the Streitwieser scale). Consequently, in this curve, logarithmic relative exchange rates (toluene = 1) rather than pKa values are plotted on the horizontal axis.

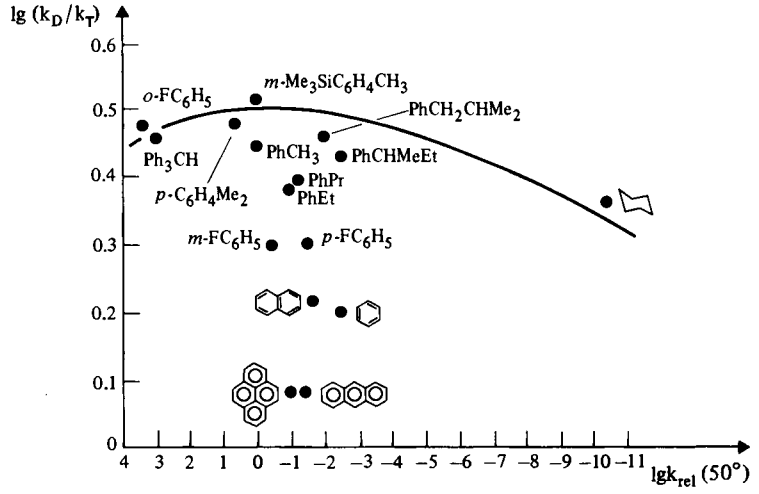


Fig. 13. $lg(k_D/k_T)$ vs. lgk_{rel} for hydrogen exchange of some hydrocarbons in cyclohexylamine/lithium cyclohexylamide. Data from Table 58.

This curve has been plotted so as to place its maximum in the vicinity of toluene lgk_{rel}. This seems to be a reasonable approach since the pKa's are 35 for toluene and ammonia in the Cram MSAD scale while the cyclohexylamine acidity should not differ much from that of ammonia.

It is evident from Fig. 13 that in a cyclohexylamine medium there is no regular dependence of kinetic isotope effect on the structure of the CH-acid. It is assumed that this is due to the fact that the exchange mechanism alters on going from one class of hydrocarbons to another. It is necessary to believe that the low kinetic isotope effect is caused not only by the internal return mechanism. In condensed aromatics, this may very well result from the fact that the compounds exchange their protons via either an addition--elimination mechanism or a mechanism involving radical anions. These possibilities have been discussed in Section II. 1c.

Table 58 prompts the following comments on the effect of solvent and structure upon k_D/k_T.

(1) The kinetic isotope effect is usually low in alcohol (methanol) and in dimethylsulphoxide/potassium tert-butoxide media in which the equilibrium DMSO + t-BuOK $\rightleftharpoons$ DIMSYL$^-$ + t-BuOH generates alcohol.

(2) The k_D/k_T values are very often higher for the lithium cyclohexylamide/cyclohexylamine and dimethylsulphoxide/DIMSYL systems i.e., the internal return mechanism probably is in this case lower than it is in hydroxyl-containing systems.

(3) In alcohol media, a high isotope effect is observed for fluorenes and some carbonyl compounds capable of forming relatively stable planar

anions with a delocalised charge.

TABLE 58

Kinetic Isotope Effect, k_D/k_T, for Hydrogen Exchange in Various CH-acids Dissolved in Various Media. In parentheses are the Values Calculated from k_H/k_D using Equation 4.

No.	Compound	LiCHA/CHA	MeONa/MeOH	NH_3NH_2K	DMSO--t--BuOK
1	2	3	4	5	6
1	CBr_3H		1.6[a](140)		
2	CCl_3H		(1.2)[b](373)		
3	CF_3H		(1.4) (371)		
4	$(CF_3)_2CFH$		(1.5) (371)		
5	$PhC{\equiv}CH$		(ca.1)[b](362)		
6	9-Fluorofluorene		1.9 (367)		
7	Fluorene	2.4[c] (355)	2.5 (352)	1.9 (354)	
8	9-Phenylfluorene		2.5 (352)		
9	$(CH_3)_2CHCN$		1.1 (381)		
10	$(CH_3)_2CHNO_2$		2.3 (381)		
11			1.3 (381)		
12			1.5 (381)		
13	$(CH_3)_2CHCOPh$		2.0 (381)	(2.0-2.6)(382)	
14			1.8 (381)		
15	$(CH_3)_2CHCOt\text{-}Bu$		2.3 (381)		
16			1.7 (381)		
17	$PhCH_3$	2.8 (279)		2.2-2.5 (329)	1.2(281) 2.8-3.1[d](330)
18	$PhCH(C_2H_5)CH_3$	2.7 (192, 333-335)			(1.6)(282)
19	$PhCH_2CH_3$	2.4 (317)			
20	$PhCH_2CH_2CH_3$	2.5 (317)			
21	$PhCH_2CH(CH_3)_2$	2.9 (317)			
22	$m\text{-}Me_3SiC_6H_4CH_3$	3.3 (317)			
23	$n\text{-}Me_3SiC_6H_4CH_3$	3.0 (317)			
24	Triptycene	2.2 (302,303)			
25	Ph_2CH_2		1.5 (342)		1.3 (331)
26	Ph_3CH	2.9 (347)	1.6[f](427) 1.3 (342) 1.7[f](427)		
27	10,10-Dimethyl-9--phenyl-9,10-dihydroanthracene		1.6 (342)		

TABLE 58 *continued*

No.	Compound	LiCHA/CHA	MeONa/MeOH	NH_3NH_3K	DMSO--t--BuOK
28	$PhCHF_2$		2.9 (367)		
29	C_6H_6	2.5[e] (317) 1.6 (315)			
30	Naphthalene(α)	1.7 (315)			
31	Anthracene (9)	1.2 (315)			
32	Pyrene (1)	1.2 (315)			
33	$1,3,5\text{-}(CH_3O)_3C_6H_3$				2.8-3.1[d] (330)
34	Fluorobenzene, ortho- meta- para-	3.0 (372) 2.0 (372) 2.0 (372)			
35	C_6F_5H		(ca.1) (368)		
36	$1,3\text{-}F_2C_6H_4$		(ca.1)(368)		
37	Nickel ocene		2.1[f](427)		
38	Carboranes				ca.1[g](76)
39	Furan				1.5(410-413)
40	Thiophene				1.3 (410-413)
41	Cyclohexane	2.3 (297)			

a) In DMSO/MeOH (1/1) plus Et_3N

b) In water

c) In methylamine

d) In DMSO/DIMSYL

e) In CsCHA/CHA

f) In t-BuOK/t-BuOH/diethylene glycol

g) In all solvents studied. [76,77,423-425]

LiCHA = lithium cyclohexylamide
CHA = cyclohexylamine
MeONa = sodium methoxide
MeOH = methanol
DMSO = dimethylsulphoxide
t-BuOK = potassium tert-butoxide

These facts, in part discussed in the Section on isotope exchange in polyaryl methanes, may be explained in the following way.

With CH-acids which form less stable (usually, pyramid-shaped) anions, the sodium methoxide/methanol basicity is not sufficiently high to ensure a high proton abstraction rate (k_1); in contrast, the inverse reaction (k_{-1}) of protonating the free or ion-paired carbanion should be fast. The forward reaction rate (k_1) increases and the inverse reaction rate (k_{-1}) decreases, on raising the basicity of the medium by changing to a lithium cyclohexylamide /cyclohexylamine or a KNH_2/NH_3 medium. It is a reasonable assumption,

therefore, that the ion-pair mechanism involving strong complexes of the type $[(R^-M^+)\ (ROH)]$ in alcohol allows the ion-pair "shutting" to become faster than is the alcohol exchange with the medium, in other words k_{-1} may become higher than k_2. This will lead to a marked increase in the contribution of the internal return mechanism. On going to more basic systems such as lithium-cyclohexylamide/cyclohexylamine or KNH_2/NH_3, the carbanion ion-pair formation rate increases steeply while the inverse reaction rate (k_{-1}) decreases. This lowers the probability of the internal return mechanism operating and increases the kinetic isotope effect.

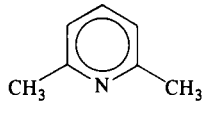
With carbanions of the fluorenyl type, the high kinetic isotope effect observed in methanol may be explained by assuming that the exchange, involving rather stable planar carbanions in a rather polar medium is significantly contributed to by free, symmetrically solvated carbanions, with a relatively high lifetime. The low kinetic isotope effect for a dimethylsulphoxide/potassium tert-butoxide system has been explained in Section II. 1 d by assuming that the proton donor is tert-butanol whose concentration is very low ($k_{-1} > k_2$ [t-BuOH]).

Unfortunately, there is very little data available to permit a comparison to be made of kinetic isotope effects of CH-acids in different media.

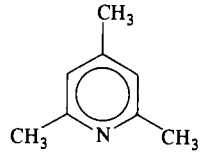
The data discussed in this Chapter demonstrate that the concept of devising a unit scale of "intrinsic" kinetic acidity which characterises C-H ionisation rates for a great number of CH-acids is far from having been achieved and, indeed, in a wide series of CH-acids several mechanisms may be involved.

Usually, published work dealing with kinetic acidity has not discussed the isotope effects, so on the basis of this data it is not possible to say whether the proton abstraction rate, or the rate of a different process, is involved.

In concluding this Section, it is interesting to discuss the reason why "anomalously" high kinetic isotope effects may arise with some compounds. A very high isotope effect has been observed in the case of the iodination of 2-nitropropane in a tert-butanol/water (6/10) system in the presence of pyridine base catalysts[445].



k_H/k_D: 24.1 (19.5;[436])



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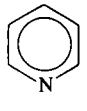


9.8

The rate-determining step in these reactions is the abstraction of a proton from the CH-acid in the presence of a base. It is noteworthy that the kinetic isotope effect (k_H/k_D) is about 24 for 2,6-lutidine and 2,4,6-collidine whereas it has its normal value for the unsubstituted pyridine.

The very high kinetic isotope effect found here indicates that the proton transfer obeys a tunnel mechanism. The mass of the proton is relatively small so the proton, as a quantized species, may permeate (i.e. tunnel) through an activation barrier. Tunnel effects for proton transfer reactions have been discussed by Bell[440] and by Caldin[446]. Bell's tunnelling criteria, alongside with a high isotope effect, are (i) a large difference between the proton and deuteron transfer activation energies (ΔEa), a low ratio of the pre-exponent factors (A_H/A_D) and (ii) non-linearity of the Arrhenius plot at lower temperatures.

Proton transfer between 2-nitropropane and 2,4,6-collidine does indeed display a high isotope effect, a high ΔEa value, and a low A_H/A_D ratio[445], k_H/k_D is 0.15 exp (3006/HT).

When there is no tunnelling the A_H/A_D ratio should be close to unity (the lowest possible value is $1/\sqrt{2}$[447]. The low A_H/A_D values were also observed when 2-nitropropane is iodinated in the presence of lutidine (A_H/A_D 0.14) or nitroethane is iodinated in the presence of 2-tert-butylpyridine (A_H/A_D 0.091) [448].

Proton transfer reactions whose Arrhenius plots are non-linear are not frequently encountered. A quantized interpretation of the non-linear Arrhenius plots observed at lower temperature was presented for the first time by Bell et al[447] and by Hulett[449] who studied the bromination of 2-carboethoxycyclopentanone in the presence of fluoride ions. The non-linear plots were also obtained in the case of proton transfer to 2,4,6-trinitrobenzyl anion in ethanol containing acetic acid or hydrogen fluoride. The deviation was of about 45% for the rate constant at +25°C to -90°C for the first reaction[450] and 120% (at -90°C) for the second reaction[451].

There remains the problem of why tunnelling does not occur in unsubstituted pyridine. Lewis et al[445] believe that the activation energy for proton transfer is a sum of two terms, the C-H bond rupture energy and the non-bonded groups repulsion energy. Where steric hindrance effects are higher (e.g., 2,6-substituted pyridines), the repulsion energy will increase and the barrier will increase steeply. The repulsion energy is very dependent on the interatomic distances, so the activation barrier is especially steep in the vicinity of the maximum and it can be overcome only with difficulty in classical mechanical terms. Consequently, the probability of tunnelling will increase.

Chapter IV

Stereochemistry of Proton Transfer

A study of the stereochemistry of proton transfer in CH-acids provides information on transition states[285]. Trisubstituted carbanions may have various configurations such as sp^3 to sp^2, depending on the substituents. Alkyl carbanions resemble ammonia or aliphatic amines in that inversion between the pyramid structures is quite fast. The H-CH angle has been calculated to be 106.8° and the inversion barrier about 5 kcal/mole in the methyl anion[452] (the CH_3 radical and, especially, CH_3^+ cation have planar structures). A seperable system of optical antipodes should have a racemisation barrier at about 16-20 kcal/mole at room temperature[453]. Consequently, racemisation is the most probably result of hydrogen exchange in alkanes.

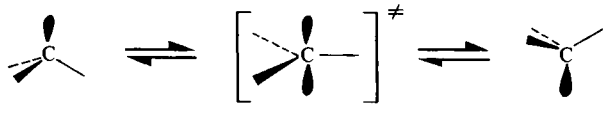
Higher energy barriers have been observed in some carbanions of peculiar structure, thus the cyclopropyl anion has been shown by calculation to have a pyramidal structure whose inversion barrier is 14.2[454] 20.85 kcal/mole[455], or 36.6[456] kcal/mole. Thus, hydrogen exchange in cyclopropane systems may be expected to result in a noticeable retention.

Racemisation barriers are affected not only by the carbanion structures but also by ion-pair formation, asymmetric solvation, aggregation, etc[285]. Even with planar fluorene carbanions, hydrogen exchange may lead either to almost complete retention or to complete racemisation, depending on the solvent and catalyst used[285]. So, the medium may play a more important role than do internal factors.

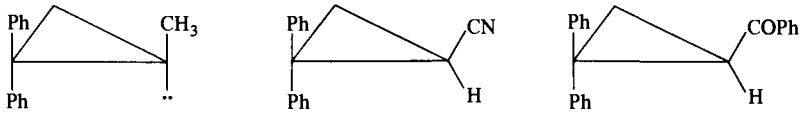
Finally, there are asymmetric carbanions stabilised by groups containing Period III elements of which RSO_2, RSO, and RS are the best studied examples. These systems display a high stereospecificity which bears no relation to the medium effect, since retention is observed even in media of high dielectric constant. These various types of carbanions will be dsicussed below under separate headings.

I. CYCLOPROPANE CH-ACIDS

The inversion of the cyclopropyl carbanion is slow compared to that of open-chain carbanions because of angular strain in the three-membered ring. The transition state for inversion (i.e. for racemisation) seems to be planar, with bond-bond angles of 120°. If one of the angles is made invariable (60°) by shutting it in a three-membered ring, the inversion barrier, naturally, will increase.



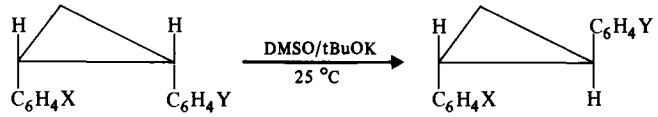
Indeed, unlike the respective open-chain compounds 1-methyl-2,2-diphenylcyclopropyl anion (I) obtained in various solvent/base systems displays a retention of 46 to 100% in its reactions[457-459]. However, these retentions were mostly obtained in solvents of low polarity, so the ion-pairs rather than a free carbanion take part in the reaction thereby strongly affecting the stereochemical course of the reaction as follows.



When the methyl group in carbanion I is replaced by groups which are capable of stabilising a negative charge by conjugation, the inversion energy of the planar transition state decreases. Thus, the 1-cyano-2,2-diphenylcyclopropane carbanion (Ia) obtained in aprotic solvents of low polarity racemises in less than 15 sec whereas carbanion I displays a marked retention under the same conditions[460]. However, hydrogen exchange in Ia dissolved in methanol, tert-butanol or a mixture of dimethylsulphoxide and methanol leads to the retention of 99.99-97.2%[461]. The high retention, and the fact that in protic solvents it is higher than in dimethylsulphoxide have been explained by assuming that the inversion barrier is increased by hydrogen bonding with the sp^3 orbital carrying the negative charge[461].

The hydrogen exchange rate is 8080 times the racemisation rate for the carbanion Ia in a methanol/sodium methoxide system at 25°C, but $k_{exchange}/k_{rac}$ is 1.37 for the benzoyl derivative (Ib). The average percentage of net retention observed for compound Ib in MeOD/MeONa is as low as 27%. This agrees with the higher ability of the COPh group, compared with nitrile group, to stabilise a negative charge (See Ch. II).

Cis-trans-isomerisation in 1,2-diphenylcyclopropanes provide additional information on base-catalysed hydrogen exchange in cyclopropane systems[464-467].



The isomerisation rate pattern in dimethylsulphoxide/potassium tert-butoxide is as follows[466].

X	H	H	p-CH_3	p-OCH_3
Y	O-F	H	p-CH_3	p-OCH_3
k_{rel}	5.4	1.0	0.15	0.05

The existence of a substituent effect which is so high (it is at the highest

with fluorine, cf. Ch. III) suggests that the cis-trans isomerisation involves a carbanion-like intermediate. Comparison of the rate of isomerisation with the rate of deuterium exchange of 1,2-diphenylcyclopropane shows that deuterium exchange in the cis-isomer which is initially rather fast, is decelerated by a factor exceeding 100 towards the end of the reaction (Fig. 14). The trans-isomer exchange rate is about 1% of the cis-isomer rate and does not depend on the reaction time[465,467].

k(cis ⟶ trans, 25°C),	sec^{-1}	5×10^{-5}
$k_{exchange}$(cis, 25°C),	sec^{-1}	1×10^{-5} (in an hour) 5.6×10^{-7} (in 141 hours)
$k_{exchange}$(trans, 25°C),	sec^{-1}	5.5×10^{-7}

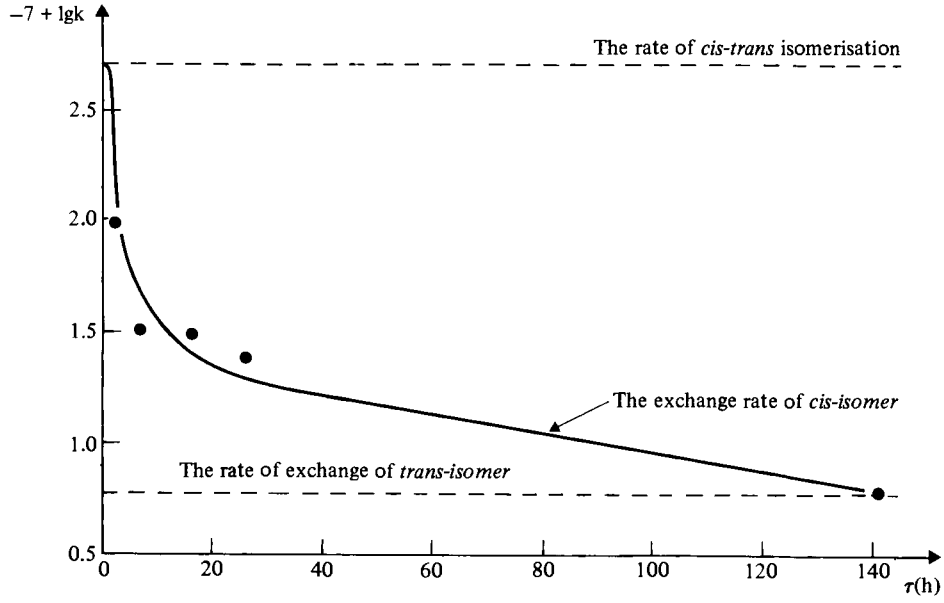
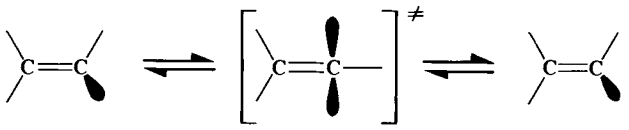


Fig. 14. Exchange rate of cis-1,2-diphenylcyclopropane vs. the exchange time; in dimethylsulphoxide/potassium tert-butoxide at 25°C

The deceleration of the rate of cis-isomer exchange is due to isomerisation resulting in an increase in the concentration of the inactive trans-compound. At the zero time, the exchange and isomerisation rates are of a very similar magnitude (Fig. 14). Consequently, exchange and isomerisation (carbanion inversion) should involve one and the same transition state. Due to isomerisation, the stereochemical result of the cis-isomer exchange will be inversion rather than retention, as is usually observed in cyclopropane systems.

II. VINYL CH-ACIDS

Vinyl anions resemble cyclopropyl anions in that their inversion barrier is increased by the unfavourable "allenic" structure.



"allenic" structure

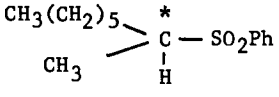
Miller and Lee[468] who studied hydrogen/deuterium exchange for cis-dibromoethylene in MeOD/MeONa and for cis- and trans-dichloroethylenes in D_2O/DONa calculated the lower boundary of the isomerisation barrier to be 25 to 35 kcal/mole in the 1,2-dihalovinyl anions. This value indicates a marked configurational stability of these anions.

To estimate the configurational stabilities of vinyl stilbene anions, Cram and Hunter[469,470] studied the hydrogen exchange and cis-trans isomerisation of stilbenes in various solvent/base systems. As occurs in the case of 1,2-diphenylcyclopropanes, the vinyl hydrogen exchange in cis-stilbene is approximately 100 times faster than it is in the trans-isomer. Cis-trans isomerisation carried out in potassium tert-butoxide/tert-butanol, potassium tert-butoxide/tert-butanol/tetrahydrofuran, or potassium tert-butoxide/tert-butanol/dimethylsulphoxide may proceed via a carbanion intermediate and/or an elimination-addition mechanism. Aryl vinyl carbanions isomerise much more readily than do alkylvinyl carbanions, because the aryl π-system may conjugate with the negative charge and thus lower the allene transition state energy. Starting from the fact that the vinyl hydrogen exchange in the cis-isomer is 10^3 times faster than in the trans-isomer, Cram and Hunter[470] proposed the mechanism of carbanion isomerisation of cis-stilbene in an alcohol/alkoxide medium, as shown overleaf.

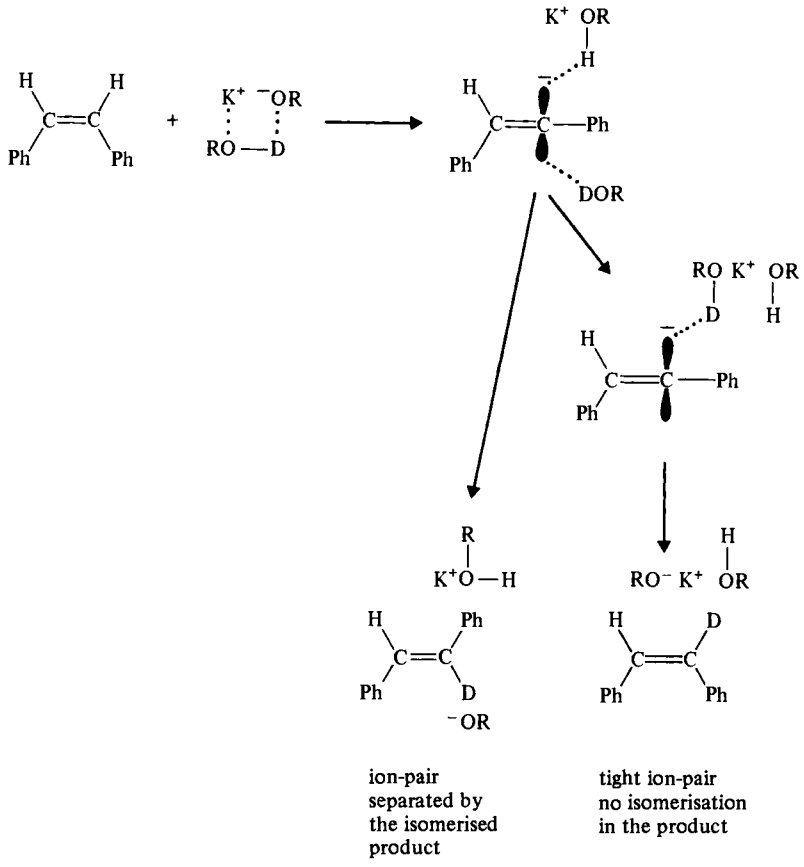
III. CH-ACIDS WITH SUBSTITUENTS CONTAINING SULPHUR

1. Sulphones

The third type of CH-acids in which stereochemistry of proton transfer is governed by internal factors rather than by ion-pair formation or asymmetric solvation embraces CH-acids whose carbanion spearhead is alpha--positioned vis-a-vis a sulphur-containing substituent. The preferential conformations of pyramid and trigonal carbanions containing SO_2 group in the alpha-position has been discussed in Chapter II (Section 6). In this system it was shown that the most stable is the conformer in which the maximal number of electron pairs and polar (S-O) bonds is in the gauche-conformation (the gauche-effect). The earliest work on the peculiar behaviour of sulphones in their isotope exchange reactions was carried out approximately a decade ago[269 270 285 472] and the results of this work can be summarised as follows: Base-catalysed hydrogen/deuterium exchange in optically active 2-octyl phenyl sulphone (II) occurs with a high retention of configuration even in solvents with a high dielectric constant.



II



The exchange/racemisation rate constant ratios obtained for the sulphone II in various basic media are shown in Table 59, these results demonstrate that although $k_{exchange}$ is higher than k_{rac}, the $k_{exchange}/k_{rac}$ ratio varies by a factor of almost 200 in varying solvent and base.

Table 59 shows that the $k_{exchange}/k_{rac}$ ratio decreases by a factor of 10 to 10^2 when quarternary tetramethylammonium hydroxide is substituted for potassium tert-butoxide in a tert-butanol solvent or when the tert-butanol

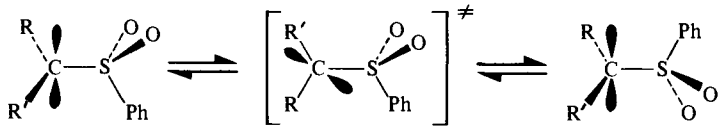
solvent is replaced by a methanol or a dimethylsulphoxide/methanol mixture. In fluorene CH-acids (planar carbanions), a similar variation of base or solvent causes the exchange rate and the racemisation rate to be close to each other (see the next Section). For sulphone II, however, the minimum $k_{exchange}/k_{rac}$ value is 10. The solvent and catalyst effects operate, evidently, in fluorenes as well as in sulphones, but the intrinsic asymmetry effect acting in sulphonyl-containing carbanions is so high that it makes the former effects insignificant.

TABLE 59

$k_{exchange}/k_{rac}$ values for Hydrogen/Deuterium Exchange in Optically Active 2-octyl Phenyl Sulphone in Various Solvent-base Systems

No	System	Temperature °C	$k_{exchange}/k_{rac}$
1	t-BuOD/t-BuOK	25	73-1200
2	t-BuOH/t-BuOK	25	139-1980
3	t-BuOH/Me_4NOH	25	22-64
4	$DOCH_2CH_2OD/ODCH_2CH_2OK$	100	25
5	$HOCH_2CH_2OH/HOCH_2OH$	100	32
6	MeOH/MeOK	100	10
7	DMSO/MeOH/MeOK	25	10

If the sulphonyl carbanion site is planar, the gauche-rule (Ch. III Section 6) will require that the structure which is the most favourable electrostatically will be the asymmetric conformation which may be "inverted" by rotation around the C-S bond.



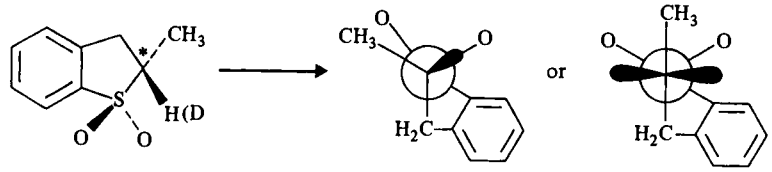
In this case the barrier to rotation is rather high because electrostatically unfavourable eclipsed conformations arise in the course of rotation.

If the carbanion site has a pyramidal structure, the racemisation will include both inversion and rotation.

An increase in planarity of alpha-sulphonyl carbanions does not necessarily lower the racemisation barrier[263], thus, exchange in 1-phenylethyl phenyl sulphone is 10^4 times faster than is exchange in 2-octylphenyl sulphone (II) [473]. Consequently, the carbanion site of 1-phenylethyl phenyl sulphone is more likely to be of the sp^2 type, in which conjugation with the phenyl group is possible. Despite the increase in planarity, however, retention in the 1-phenylethyl phenyl sulphone carbanion is higher than it is in the carbanion corresponding to sulphone II.

Probably, the carbanion site configuration in sulphonyl carbanions varies from sp^3 to sp^2 depending on the nature of the groups R and R',

A five-membered ring of compound III leads to an unfavourable conformation of the proton abstraction transition state. If a carbanion is a pyramid, its inversion will occur without any appreciable difficulties; if a carbanion is planar, then in ionising solvents it should protonate equally easily at both sides of the five-membered ring. In both cases the exchange should result in racemisation.



III pyramid; fast inversion planar

A study of hydrogen/deuterium exchange of sulphone III in MeOD/MeOK at 75°C showed that the exchange mainly results in racemisation[474]. Contributions of exchange with inversion and inversion without exchange (isoinversion) have, however, also been observed. The rate constants found for alpha-H-III are as follows (x 105 M^{-1} sec^{-1}).

Exchange with inversion	6.1
Isoinversion	1.4
Exchange with racemisation	11.7

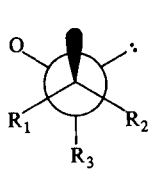
2. Sulphoxides

A study of hydrogen exchange in optically active 2-octyl-phenyl-sulphoxide ($k_{exchange}/k_{rac}$ was of about 2.4 in tert-butanol/potassium tert-butoxide, 1.0 in dimethylsulphoxide/methanol/potassium methoxide[270]) shows that exchange stereospecificity in sulphoxides is markedly lower than it is in sulphones. This may be due to the lower electrostatic effect of the lone-pair of the sulphur atom as compared with that of the polar S-O bond.

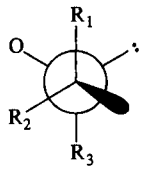
alpha-Sulphinyl carbanions contain a chiral site, sulphoxide group. Therefore, carbanions in which there are opposite configuration at the carbanion site and identical configurations at the sulphur are diastereomers rather than enantiomers (cf. sulphones). Sulphoxide carbanions are thought of as having a pyrimidal structure although this has not yet been proved[263,475] Three diastereomeric non-planar structures (IV a-c) are possible for sulphinyl carbanions. (see overleaf).

The gauche-rule states that conformation IVa should be the most stable; this agrees with theory which predicts that in the gas phase conformation IVa should be 12 kcal/mole more stable than conformation IVc and 1.6 kcal/mole

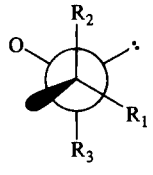
more stable than confirmation IVb[267].



IVa

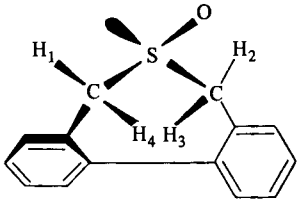


IVb

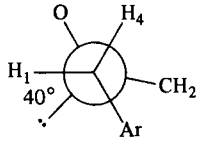


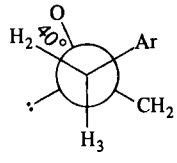
IVc

Experimentally, conformation IVc is almost always less stable while the relative stabilities of IVa and IVb depend on the nature of the solvent and the base present. The following example will demonstrate this point. In t-BuOD solvent, proton H2 in the bridged biarylsulphoxide V is exchanged faster than is proton H1 and the exchange is 200 times as fast in MeOD. On the other hand, in t-BuOD proton H4 positioned trans to the sulphur lone-pair is exchanged four times faster than is proton H3 positioned trans to the S-O dipole, but in MeOD this factor is 1/250. The Newman projections of C-S bonds and benzyl protons are represented below.



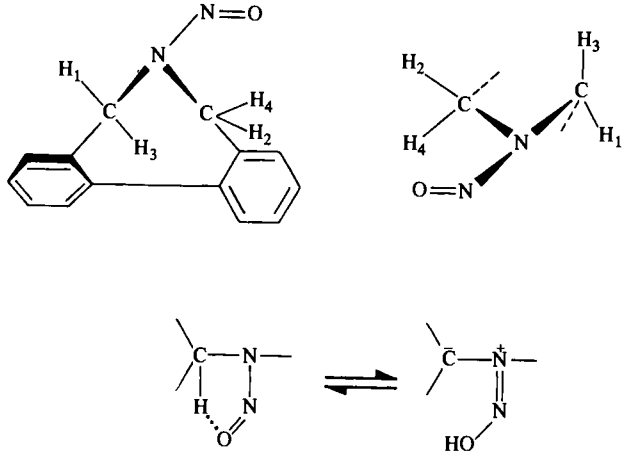
1, 11-dimethyl-5, 7-dihydro dibenzo/c,e/thiepine-6-oxide V



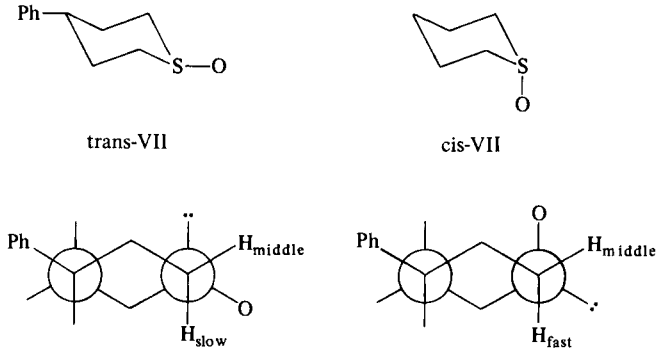


Thus, in t-BuOD, conformation IVc is more stable than is IVb whereas in MeOD the stability order is the opposite, i.e. IVb > IVc, which agrees with theoretical calculations. This stability pattern complies with the generalisation that the more stable the carbanion conformation the faster the exchange.

In N-nitro-1,11-dimethyl-6,7-dihydro-5H-dibenzo/c,e/ azepine which has a similar structure to VI, the exchange rates also differ for the four hydrogens position alpha to the N-N=O group (H1/H2/H3/H4 = 1/10/3.5/>300 in a tert-butanol/potassium tert-butoxide system[476]. In this case, however, the higher reactivity of H4 is due to co-ordination with oxygen leading to an ylide structure that readily exchanges its proton[476].



Isotope exchange of the alpha-sulphinyl hydrogen in trans- and cis-phenyl-tetranhydrothiopyran-1-oxides VII is stereoselective in water or in methanol but is not in tert-butanol or in dimethylsulphoxide-methanol[477]



The exchange rate is at its greatest for the proton (H_{fast}) lying in the gauche-position to the lone pair and in the trans-position to the S-O bond, it is at its lowest for the hydrogen (H_{slow}) gauche to the S-O bond and trans to the sulphur lone pair. The stability of the carbanion follows the following series IVb > IVa > IVc.

The product obtained by metalating stereoisomeric benzyl-α-d methyl sulphoxides (VIIa, b) with methyllithium in tetrahydrofuran followed by methyl iodide consists preferentially of the deuterium-containing isomer[478]. The scheme presented below shows that the exchange should be at its most facile when the hydrogen is gauche to both the S-O bond and the sulphur lone pair (D in VIIa or H in VIIb). This agrees with theoretical predictions.

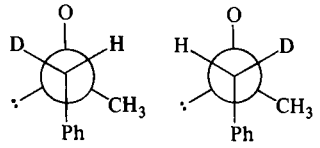
TABLE 60

Relative Stabilities of Conformations IVa, IVb, and IVc.

Compound	Method	Solvent and base	Priority	Ref.No
V	hydrogen/deuterium -exchange	t-BuOD/t-BuOK	IVc>IVb	475
		MeOD/MeONa	IVb>IVc	475
VI	hydrogen/deuterium -exchange	MeOD/MeONa	IVb>IVa>IVc	477
		D_2O/NaOD	IVb>IVa>IVc	477
		t-BuOH/t-BuOK	IVa>IVb>IVc	477
		DMSO-MeOD/MeONa	IVa>IVb>IVc	477
VII	RH RLi RCH_3	tetrahydrofuran/ methyl lithium	IVa>IVb>IVc	480,482
Substituted tetrahydro-thiophene S-oxides	hydrogen/deuterium exchange	D_2O/NaOD	IVb>IVc IVb>IVa	479
Benzyl-tert-butyl sulphoxide	RH → RLI → RD	tetrahydrofuran/ butyl-lithium	IVb>IVa>IVc	481
Benzyl p-chloro phenylsulphoxide	hydrogen/deuterium -exchange	D_2O-dioxan-sodium hydroxide	IVc>IVa	480,482
$PhSOCH_2COOH$	hydrogen/deuterium -exchange	D_2O/NaOD	stereospeci-ficity found no proton assignment made.	483
Theory	Calculation	Gas Phase	IVa>IVb>IVc	267

t-BuOK = potassium tert-butoxide
t-BuOH = tert-butanol
DMSO = dimethylsulphoxide

It is seen, however, in Table 60 that some results indicate that conformation IVb is more stable than IVa.

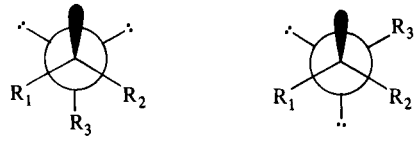


VIIa VIIb

92%	8%	39%	61%
53%	47%	30%	70%
6%	94%	20%	80%

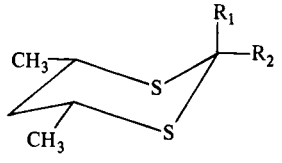
3. Sulphides

The gauche-rule and the various calculations that have been carried out[268] indicate that of the two methylsulphenyl carbanion conformers VIIIa and VIIIb, the former is the more stable.



VIIIa VIIIb

This point of view has been substantiated by a study of trans-metalation of 2-substituted cis-4,6-dimethyl-1,3-dithianes IX a-f with butyllithium[484-486]. The reaction mixture containing the dithiane lithium derivative was poured into a solution of hydrogen chloride or deuterium chloride and the products composition was studied.



IX

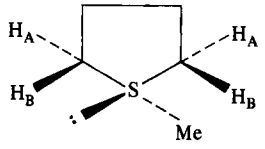
a: $R_1=R_2=H$
b: $R_1=H$, $R_2=D$
c: $R_1=R_2=D$
d: $R_1=D$, $R_2=H$
e: $R_1=H$, $R_2=t\text{-}Bu$
f: $R_1=t\text{-}Bu$, $R_2=D$

The lithium derivative of IXa when treated with deuterium chloride gives the equatorially deuterated product IXb at a yield of 99%; the IXc derivative upon reaction with hydrogen chloride, similarly gives nothing but IXd. Acid treatment of the lithium derivative of IXe (containing an equatorial tert-butyl group) results in a 99% yield of IXf whose tert-butyl is axial. These facts suggest that the molecular system under discussion prefers the conformation IXa.

4. Sulphonium Salts

Diastereotopic protons H_A and H_B in the sulphonium salt X exchange

at the rates ratio of 30/1 in $D_2O/NaOD$[484,487].

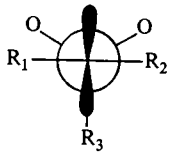


X

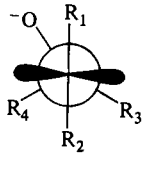
In six- or seven-membered systems similar to X, no difference has been observed between the exchange rate of the alpha-hydrogen atoms[488]. Unfortunately, conformational preference in compound X is rather indefinite because of rapid envelope ⇌ semi-chair interconversion.

5. Other Systems

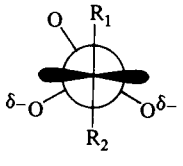
Groups such as ArSO, SO_3^-, Ar_2PO, $(RO)_2PO$, SO_2NKPh lead to insignificant stereospecificity of the alpha-hydrogen exchange[285,489]. The $k_{exchange}/k_{rac}$ ratio is 1.1 to 2.9. However, SO_2NR_2, $ROSO_2$, ArP(OK)O, and similar groups do give a high stereospecificity, $k_{exchange}/k_{rac}$ is 17 to 37 [489], even in dimethylsulphoxide. An explanation is that if a Period III element carries two electronegative substituents, the functional groups will make the carbanion asymmetric, but if it carries one or three such substituents no asymmetrisation will occur.



asymmetric



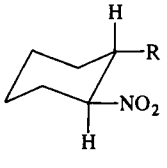
symmetric



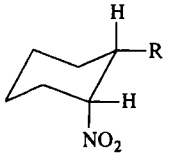
symmetric

IV. CH-ACIDS FORMING AMBIDENTAL ANIONS

Bordwell and Yee[490] measured deprotonation rates for 2-substituted nitrocyclohexane in methanol/sodium methoxide. Bordwell and Vestling[491] found that the more stable trans-2-phenylnitrocyclohexane (trans-XI, R is Ar) exchanges its acidic hydrogen 350 times as fast as does the cis-isomer.



trans-XI
(more stable)



cis-XI
(less stable)

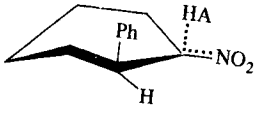
A similar effect has been observed for other cis-trans pairs and the k_{cis}/k_{trans} ratio usually correlates well with the difference between the ground state energies of the cis- and trans-conformation of 2-substituted nitrocyclohexanes. The values found for 2-arylnitrocyclohexane and for open-chain nitro compounds (1-aryl-2-nitropropanes, 0.87; cis-2-aryl-1--nitrocyclopentanes, 0.89; cis-2-aryl-1-nitrocyclohexanes 0.84; trans-2-aryl -1-nitrocyclopentanes, 1.45; trans-2-aryl-1-nitrocyclohexanes, 1.23) show that the trans-isomers are the most sensitive to the effect of the substituent in the benzene ring. This was explained by assuming that in the trans-isomers the aryl group lies closer to the acidic proton that it does in the cis-isomers or in the open-chain compounds and, consequently, the chair conformation in trans-2-aryl-1-nitrocyclohexanes is somewhat deformed[490].

However, the k_{cis}/k_{trans} ratio for the stereoisomeric pairs of 2-methyl and 2-phenyl-1-nitrocyclohexanes exceeds the value expected on the basis of the difference between the cis- and trans-conformation energies in XI by a factor of about four. Bordwell and Yee[490,492] assumed that this was due to spatial hindrance towards proton abstraction exerted by the substituent in position 2.

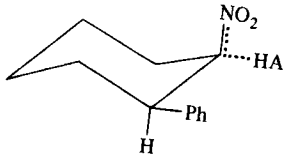
Exo-protons in the stereoisometric pairs of 5-nitrobicyclo/2.2.1/heptenes-2 and 2-nitrobicyclo/2.2.1/heptanes are exchanged faster than are the endo-protons, which is also explainable in terms of spatial hindrance.

During the inverse reaction involving the protonation of ambidental cyclohexane nitronate ions, the proton enters on the same side on which it is abstracted during deprotonation; it is clear that the resulting nitro compounds are in energetically less favourable conformations[492,493]. The same is true for the protonation of enolate ions of 2-substituted cyclohexanones[494,495].

Bordwell and Yee[492] believe that the transition states for the protonation of 2-arylcyclohexane nitronate and of 2-aryl-1-nitrocyclohexane are similar. The C-H bond is in part formed, the C=N bond in part decomposed. If protonation occurs on the equatorial side, there will not be any excessive strain in the system. On the other hand, when a proton donor attacks the axial side, the nitro group should become pseudo-equatorial and the phenyl group should take the pseudo-axial position in which it will hinder attack by the proton donor.



transition state for axial deprotonation (spatial interaction of HA and Ph)

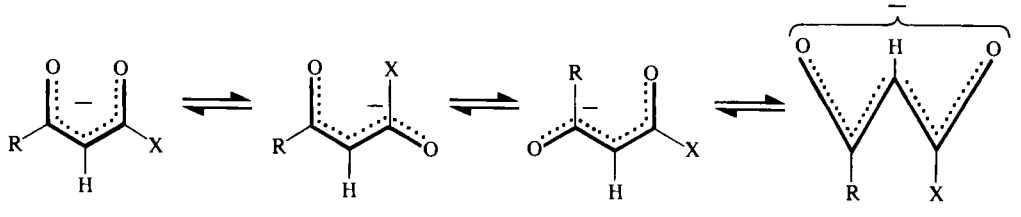


transition state for equatorial deprotonation (no Ph/HA steric interactions)

Studies of the substituent effect in substituted acetoacetic esters on the kinetics of proton transfer also emphasises the prevailing role played by spatial hindrance created by bulky alkyl groups[496].

Regarding the stereochemistry of hydrogen exchange in ambidental systems, Wilson[497] and Ingold et al[498] found as early as 1936 that deuterium-exchange and racemisation rates are equal for optically active 2-benzoylbutane in a dioxan-D_2O-NaOD system. This was explained by assuming that the reaction proceeds via a proton abstraction step leading to the formation of a planar enolate ion. That the exchange and racemisation rates are equal was later verified by a study of a great number of carbonyl compounds such as alpha-benzoyl-, alpha-dimethylcarbamoyl-, alpha-(trimethylpyruvyl)--ethylbenzenes and beta-(diethylcarbamoyl)-propylbenzene[499,500] which are capable of forming planar ambidental anions. These compounds capture a proton by their oxygen function faster than by the carbon atom. The next step, which is hydrogen exchange in the enols, should be faster than is the enol to ketone transformation. This is the necessary condition for the racemisation and exchange rates to be equal[285].

Zaugg and Schaefer[501] who studied the ultra-violet spectra of beta-keto-aldehyde anions assumed that in solution there was an equilibrium between four conformations of the ambident anions: U-shaped, cis- and trans-sickle-shaped, and W-shaped conformation (X = H).



They found that the W- and S(trans)-species were more stable in aprotic solvents, the U-shaped ones in protic solvents. However, recent work[502-505] on ion pairing of beta-keto ester alkali enolates (X = OR in above equation) showed that the W- and S(trans)-species, stabilised with intermolecular hydrogen bonding, are more stable in methanol, a solvent favouring the dissociation of ion-pairs. The U-forms were found only in dipolar aprotic solvents such as dimethylformamide and dimethylacetamide, the S(cis)-species were not found at all. The equilibrium presented in equation (1) depends on the counter-ion, i.e. on the extent of ion-pairing. Lithium salts of beta-keto aldehydes in dimethylformamide, dimethylacetamide, methanol, ethanol, or water are almost exclusively in the U-conformation, whereas the potassium salts are W- and S(trans)-shaped. This is due to the fact that the U-forms are chelated with the lithium cation whose size is such that it does not deform the planar ambidental system[505].

There is no doubt that the equilibrium (equation 1) should affect the stereochemistry of oxygen protonation in alkali enolates since the enols, before they rearrange to beta-dicarbonyl compounds, are in the form of cis- and trans-isomers. This effect has not, however, been studied further.

On the other hand, O-alkylation of acetoacetic ester alkali enolates is known to lead to the formation of stable alkyl vinyl ethers and this is directly concerned with the various conformations of alkali enolates when in the form of ions or ion-pairs[506].

V. FLUORENE CH-ACIDS

Fluorene and similar types of CH-acids form symmetric or almost symmetric, (i.e. planar or almost planar), carbanions whose stability is due to the aromatic π-system built up.

9-Substituted fluorenes may be obtained in the form of optical isomers; their 9-hydrogens are quite acidic, so they are useful for the study of the stereochemistry of isotope exchange.

It is known that in ambidental ions the negative charge is mainly localised on the oxygen atom and the ions, therefore, are protonated at the oxygen to form neutral molecules of enols followed by the enol to ketone rearrangement. In anions of the fluorene type, in contrast, the charge is constantly (partially) localised on the 9-carbon. Consequently, hydrogen exchange in the systems, in solvents of low or moderate polarity, may or may nor lead to complete racemisation, as occurs in the case of ambidental anions discussed in the preceding Section. For media of moderate polarity, much data exists to demonstrate that the exchange involves ion-pairs (or asymmetrically solvated carbanions, when a free lyate anion is the base which abstracts proton) rather than free carbanions.

The stereochemistry of hydrogen exchange in fluorene systems has been studied by Cram et al[500,507-513]. This work revealed important correlations in the stereochemistry of ion-pairs and led to the important concepts of isoracemisation, isoinversion, the conducted tour mechanism, and others.

Cram assumed[285,514] that four limiting $k_{exchange}/k_{rac}$ ratios are possible if the exchange follows a single stereochemical route strictly.

$k_{exchange}/k_{rac} \rightarrow 0$	100% isoracemisation
$k_{exchange}/k_{rac} \rightarrow 0.5$	100% inversion
$k_{exchange}/k_{rac} \rightarrow 1$	100% racemisation
$k_{exchange}/k_{rac} \rightarrow \infty$	100% retention.

In reality, any hydrogen exchange reaction follows several courses simultaneously and the total stereochemistry is governed by the individual contributions of these different courses. Stereospecific steps of the process for a CH-acid with a deuterated medium may be pictured in the following way (the symbols H and D denote the starting compound and the exchange product, and "+" and "-" the signs of optical rotation)[510].

$H_+ \xrightarrow{k} D_+$	$H_- \xrightarrow{k} D_-$	exchange with retention
$H_+ \xrightarrow{k} D_-$	$H_- \xrightarrow{k} D_+$	exchange with inversion
$H_+ \xrightarrow{k} H_-$	$H_- \xrightarrow{k} H_+$	inversion without exchange (isoinversion)
$D_- \xrightarrow{k} D_+$	$D_+ \xrightarrow{k} D_-$	inversion after exchange

The specific reaction rates, k_1, k_2, k_3 and k_4, referred to above can be found from the following kinetic equation[510],

$$\alpha=\left[\frac{\alpha_o}{(\mathcal{Y}-1)+\Psi}\right]\left[(\mathcal{Y}-1)\exp\left[-\theta(1-\Psi)t\right]+\Psi\ \exp\ (-\theta\mathcal{Y}t)\right]$$

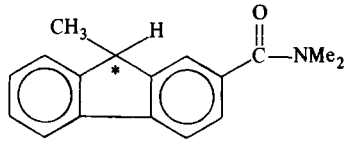
where α is the rotation at the moment t, α_o is the rotation at the time zero $\mathcal{Y} = k_4/(k_2+k_3)$, $\Psi = (k_2-k_4)/2(k_2+k_3)$, $\theta = 2(k_2+k_3)$.

The individual rate constants calculated for the compound XII in potassium methoxide/methanol or tert-butanol/potassium phenoxide are listed in Table 61.

TABLE 61

Hydrogen/Deuterium Exchange Steps for XII in Various Solvent/Base Systems, 25°C[510 511].

System	Step	10^5xK, $M^{-1}sec^{-1}$
CH_3OD - CH_3OK	k_1	302
	k_2	302
	k_3	26
	k_4	51
t-BuOD-PhOK	k_1	1.21
	k_2	0.56
	k_3	0.046
	k_4	4.48

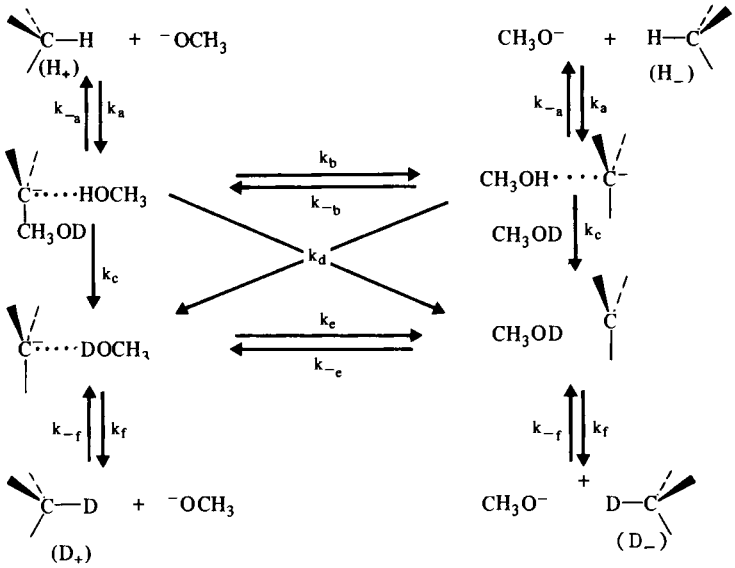


XII

The data in Table 61 show that the rates of exchange with inversion and of exchange with retention are equal to unity. The experimental value, 0.92, is, however, lower because of a contribution by the isoinversion mechanism (k_3 is 0.26). The whole process as it occurs in methanol may be represented as shown overleaf[511].

Experiment shows that for compound XII in methanol $k_1 = k_2$. In this case the isoinversion may contribute in two modes[511]. (1) When $k_c = k_d$ the constants k_b and k_{-a} (or k_e and k_{-f}) should be sufficiently high to allow isoinversion to compete with exchange. (2) When $k_c \neq k_d$, then k_b and k_{-a} (or k_e and k_{-f}) should be higher than k_c or k_d. Thus, the contribution of the isoinversion will increase with an increase of the contribution by the internal return mechanism (Ch. III). In the case under discussion, however,

no internal return mechanism operates and the slow step is the reaction k_a while k_{-a} is low compared with k_c and k_d.

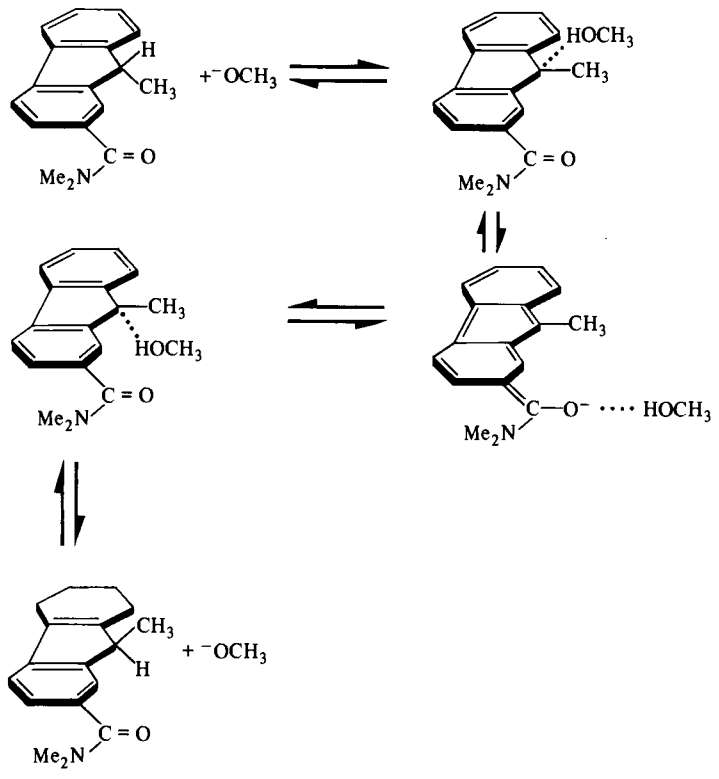


This follows from a rather high kinetic isotope effect for racemisation, (k_H/k_D 6.6). When k_{-a} is low, the contribution of isoinversion may be thought of as sensible only if it is assumed that k_b is at least comparable with k_c and k_d (whichever of the latter constant be higher). In other words, the intramolecular reorganisation of the carbanion/methanol associate should be as fast as is the exchange with the solvent.

Cram et al[511] believe that the isoinversion may be described in terms of a conducted tour mechanism, without including the carbanion free from hydrogen bonding with a methanol molecule. The molecule leaves the carbanion site for the amide group, the moves at the back side to position 9 again, without separating from the anion. This may be illustrated by the overleaf scheme[285].

In t-BuOD/PhOK solvent, the rate of exchange with retention is twice the rate of exchange with inversion ($k_1>k_2$ see Table 61) whereas, due to isoinversion the experimental $k_{exchange}/k_{rac}$ ratio is about unity[511].

Isoinversion leads to the isoracemisation (racemisation without exchange) of optically active CH-acids. The mechanism of isoracemisation was described in general terms in Chapter III, Section I. This mechanism operates when an optically active acid is treated with base in the absence of any proton donors; e.g., optically active 2-(N,N-dimethylcarboxamido)-9-methylfluorene undergoes isoracemisation when heated up to 145°C with an 0.5 M triethylamine solution in dry tetrahydrofuran[285]. Isoracemisation gives very low $k_{exchange}/k_{rac}$ ratios.



The $k_{exchange}/k_{rac}$ pattern depends on the following factors: (i) the nature of the substituent in the fluorene aromatic rings, (ii) the position of the substituent, (iii) the base catalyst used and (iv) the solvent/base system[512].

A substituent capable of shifting the negative charge of the carbanion towards its electronegative atom usually favours isoinversion. Apart from the dimethylcarboxamido group discussed above, nitro groups[500, 508, 509], nitrile groups[509,515], carboxyl groups[512], ester groups[516] and others are among substituents of this kind. Table 62 lists the effects of substituent on the total exchange stereochemistry for the compounds XII and XIII.

The data in Table 62 demonstrates than an increase in the (-M) effect of the electronegative group leads to a decrease in the $k_{exchange}/k_{rac}$ ratio to 0.1, which means that the main route is isoinversion leading to racemisation of the starting compound and of the exchange product.

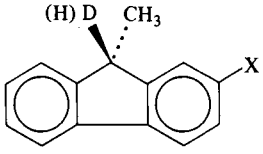
In contrast, alkyl[282,517], alkenyl[517], aryl and haloaryl[518] groups in optically active CH-acid do not favour isoinversion in their reactions with

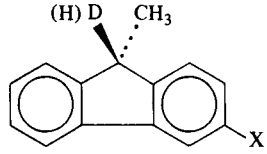
alkoxides or trialkylamines. In non-polar media of the tert-butanol type, the exchange results in retention. These facts give appreciable support to the idea that isoinversion obeys the conducted tour mechanism within the ion-pair. The mechanism may operate not only in fluorene but also in other systems of an appropriate structure. Jeager et al[518] have suggested that the 4-pyridyl group may favour isoinversion as illustrated overleaf.

TABLE 62

Substituent Effects upon Total Overall Stereochemistry of Base-catalysed Hydrogen Exchange in 9-methylfluorene[512]

Compound	$k^{rel}_{exchange}$, fluorene=1		$k_{exchange}/k_{rac}$		
	Methanol/ potassium methoxide	tert-butanol/ tripropylamine	tert-butanol/ tripropyl-amine	tetra-hydrofuran/ propylamine	methanol/ potassium methoxide
9-Methylfluorene	0.26	-	-	-	-
Fluorene	1.00	-	-	-	-
XII	6.22	-	5.7	> 56	0.82
XV	13.2	13.2	0.14	1.4-2.5	1.2
XIII	-	375	0.1	-	-
XIV	-	905	0.1	-	-
XVI	-	5500	<0.1 (t--BuOH--THF)	1.0	





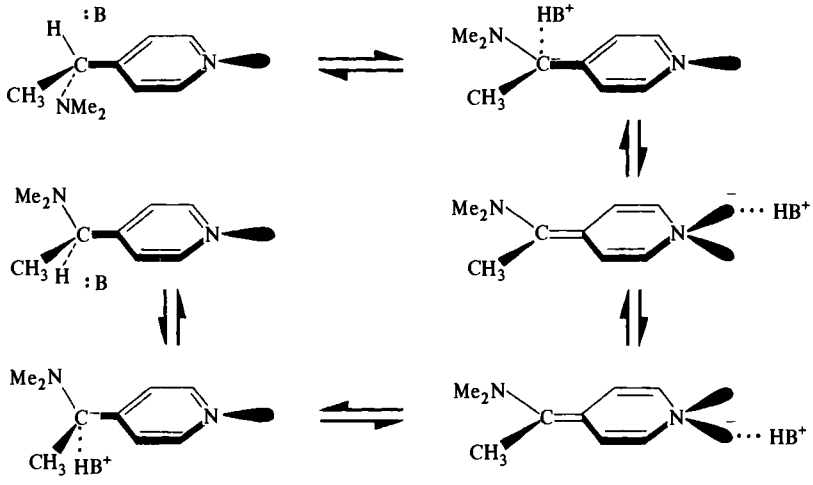
XII : X=$CONMe_2$
XIII: X=CN
XIV : X=NO_2
XVII: X=CH_3
XVIII: X=I
XIX : X=$\overset{+}{N}Me_3I^-$

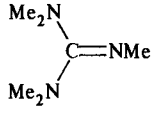
XV : X=$CONMe_2$
XVI : X=COO^-
XX : X=I

The base, together with the proton abstracted from the benzyl carbon, move along the π-electron face of the molecule towards the nitrogen and, along the opposite face, backwards to the carbon.

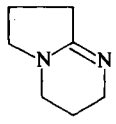
Another mechanism may operate when the reaction is catalysed with bases in whose positively charged conjugate acids the charge is delocalised, e.g., pentamethylguanidine XXI or 1,5-diazabicyclo/4.3.0/-nonene-5 XXII[513], (see overleaf).

In a tert-butanol solvent, the ratio $k_{exchange}/k_{rac}$ is less than unity not only for (-M) substituted compounds XII and XV but also for methyl- and trimethylammonium-substituted 9-methylfluorenes.





XXI



XXII

In this case, there is no need for the substituents which can "lead" the cation along the molecule. The explanation is evident: if both the anion and the cation of the ion-pair have planar delocalised structures, they may "slide" rather easily over each other in the contact ion-pair. If the cation slides away from the anion, it may return to the ion-pair on the opposite side, and this will lead to isoinversion. Cram et al[513] assumed that exchange in systems occurs via intimate ion-pairs.

The effect of solvent upon the stereochemistry of hydrogen exchange was studied by Cram[285] in detail with compound XII. Some of his results are summarised in Table 63.

Table 63 demonstrates that, depending on solvent and base used, the exchange in Compound XII may lead to either high retention or to complete racemisation. The reaction with retention of configuration, according to Cram, might proceed via three mechanisms.

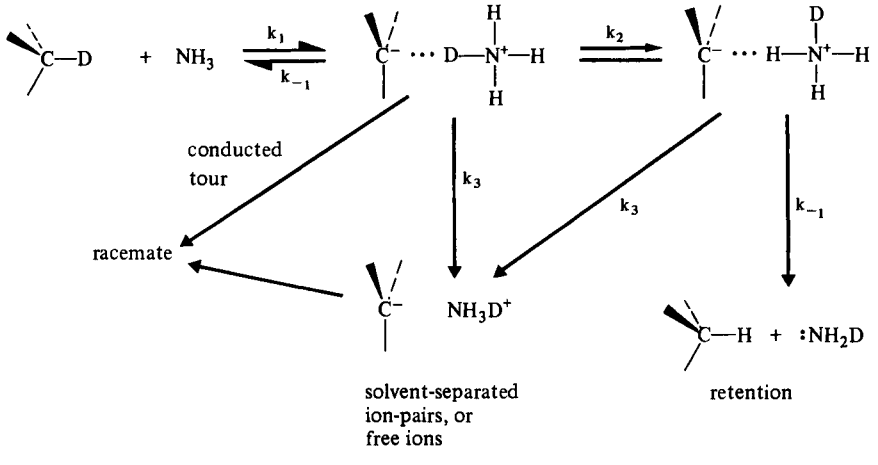
The first mechanism, with the $k_{exchange}/k_{rac}$ ratio being between 1 and 150, holds in the case of ammonia and primary or secondary amine catalysts (Nos 1-6, Table 63), shown overleaf.

TABLE 63

$k_{exchange}/k_{rac}$ values for Base-catalysed Hydrogen Exchange in Compound XII[285].

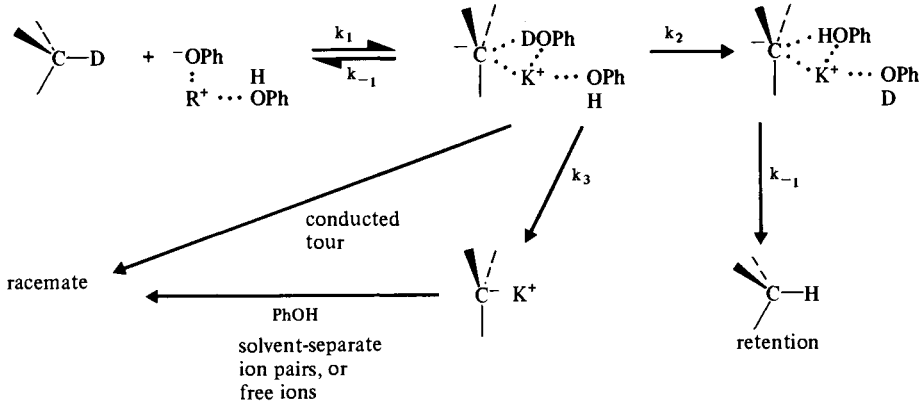
No.	Solvent	Base	Temperature °C	$k_{exchange}/k_{rac}$
1	tert-butanol	ammonia (0.8 M)	200	above 50
2	tetrahydrofuran	ammonia (0.3 M)	145	148
3	tetrahydrofuran	ammonia (4M)	25	ca. 2
4	tetrahydrofuran	propylamine	145	above 56
5	tetrahydrofuran	propylamine	145	above 9
6	dimethylsulphoxide	ammonia	25	1.0
7	benzene/phenol 10%	sodium phenate	75	18
8	benzene/phenol 10%	$PhONMe_4$	75	1.0
9	tert-butanol	tripropylamine	200	above 6
10	tert-butanol	potassiumtert-butoxide	25	1.0
11	tert-butanol	Potassiumphenate	25	1.0[510]
12	MeOD	potassium methoxide	25	0.92[510]
13	Methanol	tripropylamine	75	0.65
14	Methanol	potassium methoxide	25	0.69
15	Methanol/water	tripropylamine	75	0.78
16	diethylene glycol	triethylamine	50	0.94
17	tetrahydrofuran/ tert-butanol/ tripropylamine	tripropylamine	20	0.1 a)

a) for 7-nitro-2-demthylcarboxamido-9-methylfluorene-9-d.



In solvents of low polarity, such as tert-butanol or tetrahydrofuran, the ion-pair dissociation to free ions is weak, so the retention is high. The high dielectric constant of dimethylsulphoxide makes dissociation occur at a greater rate than the ammonium rotation within the ion-pair, and the $k_{exchange}/k_{rac}$ ratio is unity (Table 63). An increase in the ammonia concentration in tetrahydrofuran increases the concentration of the ion-pair in the solution, therefore the rate of dissociation should increase (the internal rotation rate remains unaffected) and this should lower the value of the $k_{exchange}/k_{rac}$ ratio, which is in accord with experiment (Table 63).

The second retention mechanism was observed in a benzene plus phenol (proton donor) plus potassium phenoxide (base) system. The ion-paired ammonium is now replaced by potassium ion solvated by two molecules of phenol.



This mechanism agrees with the fact that when tetramethylammonium phenoxide replaces potassium phenoxide the $k_{exchange}/k_{rac}$ ratio decreases from 18 to 1 (Nos 7, 8, Table 63). This also suggests that racemisation is mainly due to solvent-separated ion-pairs and free ions rather than to a conducted tour within intimate ion-pairs.

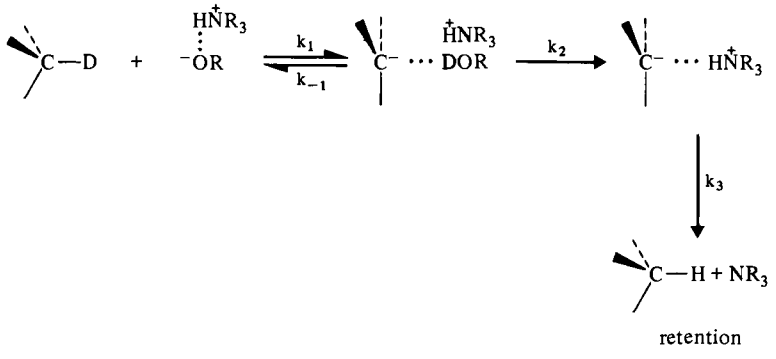
The third retention mechanism operates in the case of tertiary amine catalysis in media of low polarities (No 9, Table 63). A solution of trialkylamine in tert-butanol is believed to contain a small amount of a very strong base, R_3NH^+ $^-OBu\text{-}t$, and that this is the real catalyst involved in the exchange[285].

Consequently, retention is due to the formation of ion-pairs in which the protonation is faster on that side of the planar carbanion from which deuterium is split off.

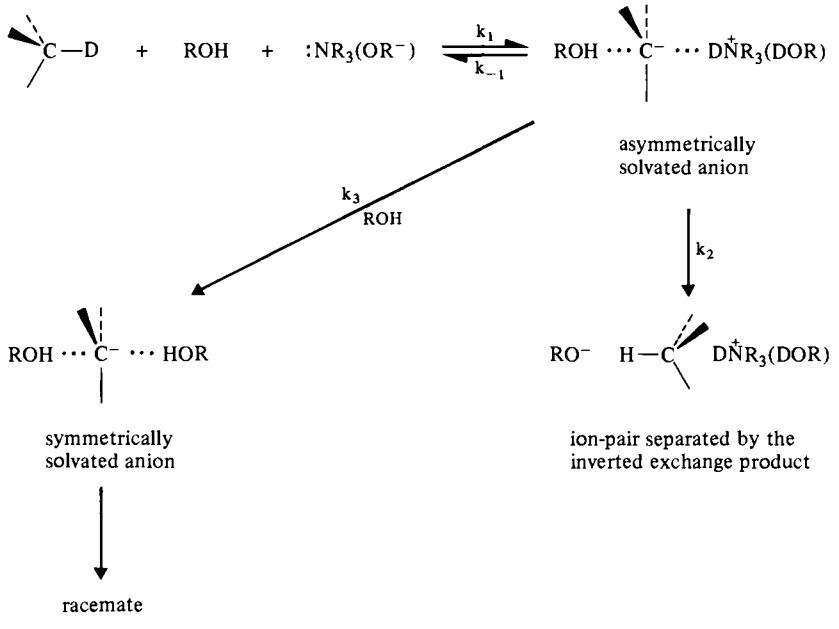
The $k_{exchange}/k_{rac}$ value for compound XII is less than unity in the systems at the bottom of Table 63. This low ratio may be due to the simultaneous occurence of inversion and retention and also to the contribution of isoinversion. In these cases $k_{exchange}/k_{rac}$ is not so informative of the exchange mechanism unless each of the individual stereospecific rate constants

are known (Table 61).

Third mechanism



A priori, the inversion mechanism for a polar alcohol/tertiary amine (or alkoxide) system (Nos 11-17, Table 63)[285]. may be represented as follows.

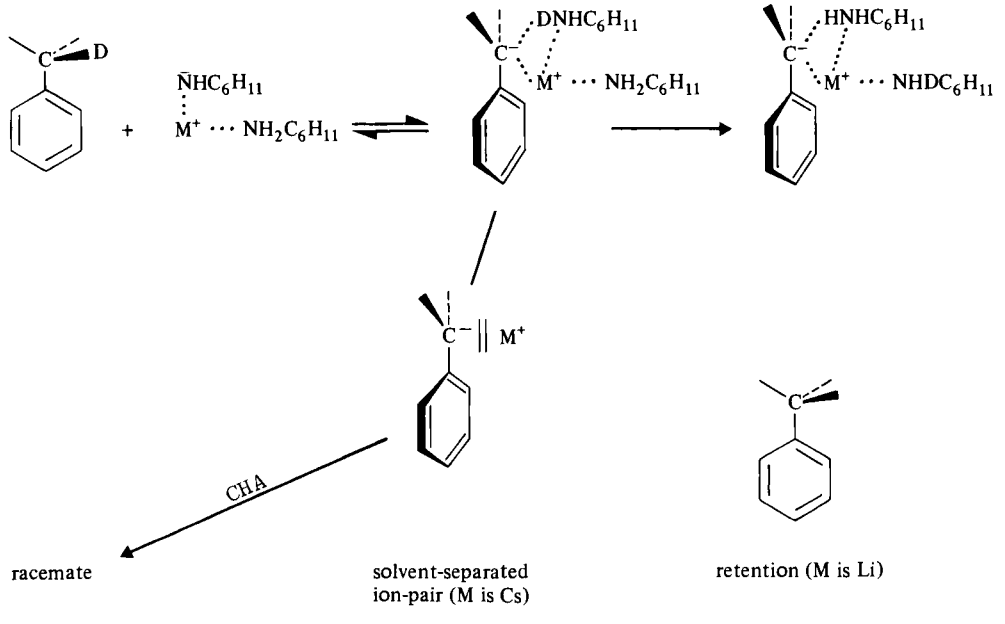


The above scheme describes two simultaneous processes: the amine or the alkoxy anion makes the C-D deuterium split off, and the resulting carbanion is solvated on the opposite side by hydrogen bonding with a solvent molecule. The resulting planar carbanion will be hydrogen-bonded with a solvent molecule on its rear side and with R_3ND^+ or a deuterated solvent molecule on its front side. Thus, deuterium can be caught only on the front side, on the side of its initial residence, thereby retaining the configuration of the original compounds, whereas the proton may be caught only on the rear side leading to inversion in the exchange product.

VI. BENZYL CH-ACIDS

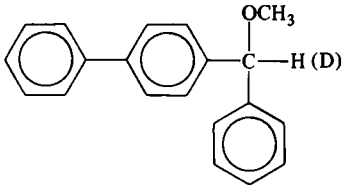
It was shown in Chapter III that benzyl hydrogen exchange stereochemistry in a cyclohexylamine/lithium (or caesium) cyclohexylamide system depends on the metal cation present. Within lithium cyclohexylamide, a 82% retention is observed whereas caesium cyclohexylamide leads to complete racemisation[317,339]. An explanation by Streitwieser and Caldwell[317] was that a four-centred transition state operated in the former case and a linear one in the latter.

Another assumption is that lithium cyclohexylamide creates intimate ion-pairs in which the lithium-carbon bond is, to a degree, retained whereas caesium cyclohexylamide results in solvent-separated ion-pairs.

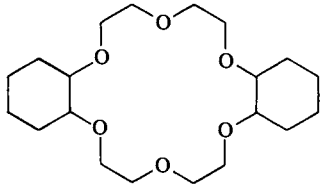


Other optically active benzyl systems containing methoxy, nitrile or CF_3 groups in the alpha-position were studied by Cram. He showed that the rate of exchange with retention exceeds the rate of exchange with inversion, thus $k_{exchange}/k_{rac}$ is 33 at 116°C[5,9] and 46 at 70°C[520] for compound XXIII in a

tert-butanol/potassium tert-butoxide system. When perhydrodibenzo/18/crown--6-ether (XXIV) is added to the system the proton transfer rate is increased (i.e., both exchange and racemisation rates rise) by a factor of 10^3 to 10^4 and, also, this leads to complete racemisation ($k_{exchange}/k_{rac}$ is about unity).

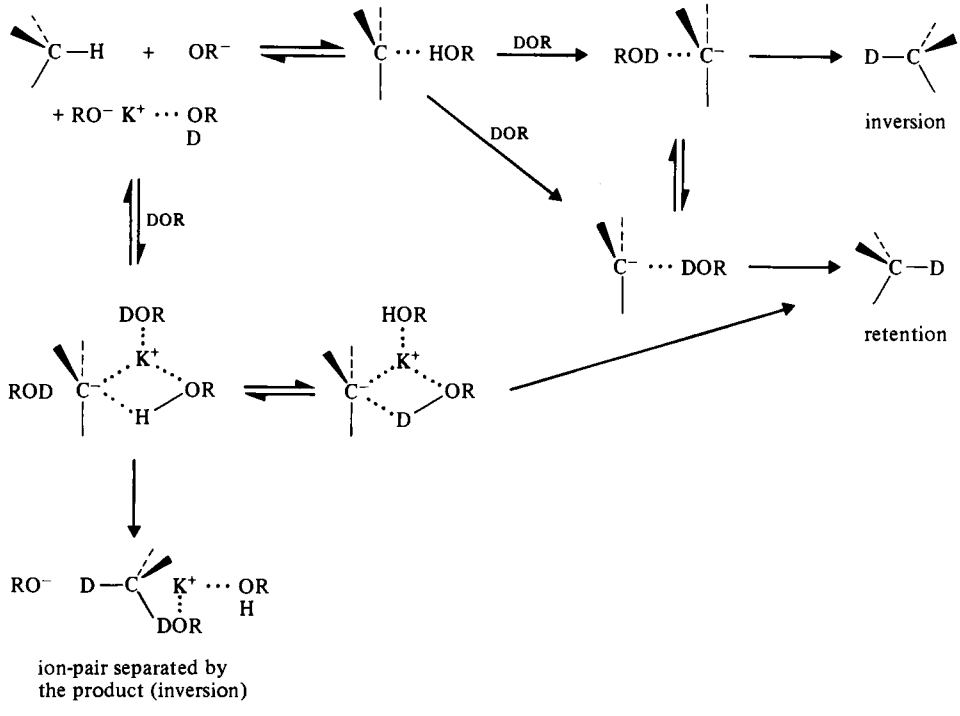


XXIII



XXIV

Cram and Kollmeyer[519] assumed that the retention was due to the ion-pair mechanism involving a four-centred cyclic transition state while the inversion proceeded in two ways: via free base ions (their contribution should not be too high in a solvent of low polarity, such as tert-butanol) and via ion-pairs separated by the reaction product.



This scheme explains the crown-ether effect. A crown ether holds the potassium cation in a strong six-co-ordinate complex whose potassium ion can no longer co-ordinate to the solvent or the carbanion site. As a result, the reaction mainly proceeds via potassium-free anions (the crown-separated ion-pairs RO^-K^+ and R^-K^+) and the $k_{exchange}/k_{rac}$ is close to unity.

The $k_{exchange}/k_{rac}$ ratio found for alpha-phenylbutyronitrile varies from 1 to 0.05 depending on the solvent/base system used[509,521]. Table 64 lists the Cram data; three groups of compounds may be identified based on the ranges of $k_{exchange}/k_{rac}$ value.

TABLE 64

$k_{exchange}/k_{rac}$ for Reactions of EtCHD(Ph)CN in Various Solvent/base Systems, 25-116°C,[509 521].

No.	Solvent/base system	$k_{exchange}/k_{rac}$
GROUP 1		
1	MeOD	1.02
2	Tetrahydrofuran/dipropylamine	1.00
3	Dimethylsulphoxide/methanol/potassium methoxide	0.98
4	Ethylene glycol/potassium bicarbonate	0.87
5	Methanol/tripropylamine	0.84
GROUP 2		
6	Benzene/phenol/potassium phenate	0.76
7	Tert-butanol/potassium tert-butoxide	0.68[a)]
8	Cyclohexane-t-BuOD/t-BuOK	0.50
GROUP 3		
9	t-BuOD-$(Me_2N_2)_2C{=}N^+DMe/(Me_2N)_2C{=}NMe$	0.22
10	Tert-butanol/tripropylamine	0.20
11	Tetrahydrofuran/tert-butanol/tripropylamine/$PR_3N^+HI^-$	0.19
12	Tetrahydrofuran/tert-butanol/tripropylamine/ quarternary ammonium iodide[b]	0.09
13	Tetrahydrofuran/tert-butanol/tripropylamine[b]	0.05

a) Crown ether additives raise $k_{exchange}/k_{rac}$ to 1[521].

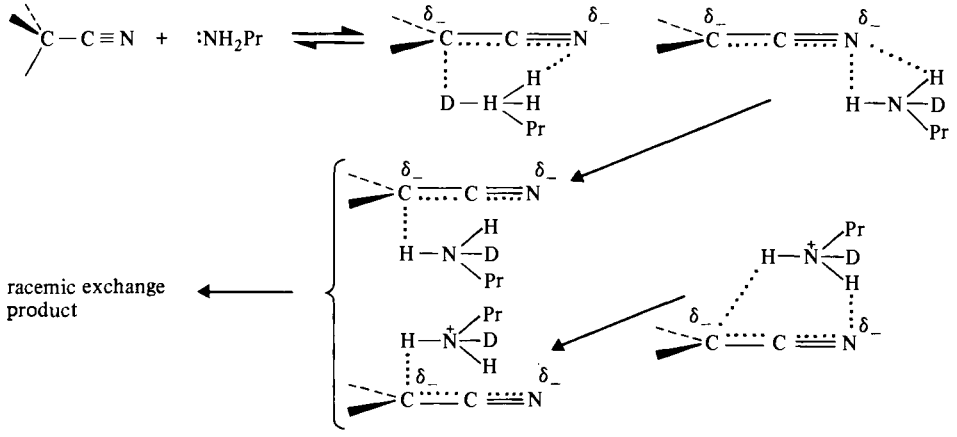
b) 1.5 mole/l t-BuOH (ca. 7.5%)

$(Me_2N)_2C{=}NMe$= pentamethylguanidine.

The first group (Nos 1-5) embraces the systems whose exchange results in a 80 to 100% racemisation. A feature of this group is that it includes rather polar media formed by proton-donor polar solvents (Nos 1, 3-5). Polar solvents favour the ionisation of ion-pairs and thus racemisation, there is an equal probability that a free planar carbanion may capture solvent on any side of its plane. Where the exchange still proceeds via ion-pairs and a contribution of this mechanism seems to be always present, Cram[285] felt that

the following process operated. Consider the ion-pair formed by alpha--deutero- alpha-phenylbutyronitrile and the complex cation that either includes a proton donor (NH_3D^+, RNH_2D^+, R_2NHD^+). In terms of the conducted tour mechanism, the rotation of the cation and of the anion in the ion-pair should proceed at comparable rates. An assumption of this kind may explain the complete racemisation observed in the nonpolar solvent, tetrahydrofuran (No.2 in Table 64).

The crucial point is, probably, the nature of the base, propylamine, whose conjugate acid, $PrNH_2D^+$ is formed from via proton abstraction from alpha-deutero-alpha-phenylbutyronitrile and which is a considerably better donor of protons than deuterons.



In tetrahydrofuran/tertiary amine systems (Nos. 10-13 Group 3 Table 64), the conjugate base Pr_3ND^+ is no longer a proton donor and the exchange can start only after Pr_3ND^+ in the ion-pair has been substituted by a cation-donor of proton (such as the cation formed via Pr_3ND^+ + t-BuOH → Pr_3NH^+ + t-BuOD). The conducted tour process causes the rate of racemisation to markedly exceed the rate of the exchange in the ion-pair, in accord with experiment.

A crown ether added to system No. 7 (Table 64) leads to complete racemisation while a pentamethylguanidine base leads to significant inversion (No. 9 Table 64), conjugate acid of this compound has a considerably delocalised positive charge.

Consequently, the data in Table 64 can be fairly well explained in terms of the ion-paired conducted tour in nonpolar media and the competition between the ion-pair and the ionic mechanisms in polar media. A role is played also

by the nature of base-catalyst.

Among other CH-acids of a similar type, only alpha-deutero-alpha-trifluoro--methylpropylbenzene[522] and alpha-triphenylmethylpropionitrile[285] have been studied in any detail. The results obtained fit in qualitatively with those discussed above for the exchange occuring in alpha-phenylbutyronitrile.

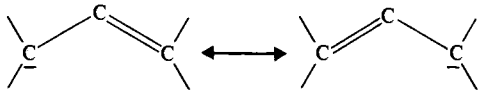
VII. PROTON TRANSFER ACCOMPANIED BY RE-ARRANGEMENTS IN UNSATURATED SYSTEMS.

This Section deals with proton transfer accompanied by re-arrangements leading only to migration of the double bond in an unsaturated CH-acid, without affecting the carbon skeleton. Alkyl or aryl migrations (the Stevens, Witting, Sommelet, Favorsky, benzyl re-arrangements, etc.) are not included in this discussion. In these re-arrangements, a base does abstract a proton from a CH-acid, but no inverse proton transfer to the carbanion occurs while, instead, the negative charge is stabilised by migration of an organic group to the anion spearhead. Therefore, the processes come under the heading of carbanion, rather than CH-acid chemistry. Re-arrangements of all types have been reviewed by Cram[285].

1. Intramolecular Proton Transfer

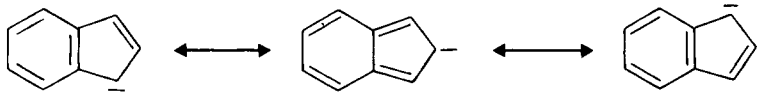
Base catalysed re-arrangements in unsaturated CH-acids involve ambidental or polydental anion intermediates.

With ambidental systems, intramolecular proton transfer can result from 1,3 migration exclusively whereas in polydental systems both 1,2 and 1,3 intramolecular proton shifts are possible.



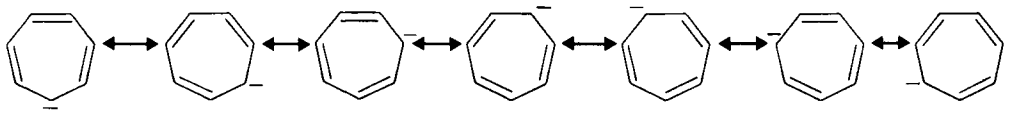
(two hydrogen bonding centres)

Polydental anions are formed by indene CH-acids (three hydrogen bonding centres).



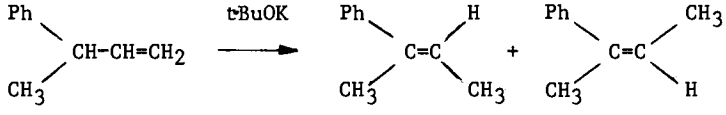
cyclopentadiene CH-acids (five hydrogen bonding centres).

and cycloheptatriene CH-acids (seven hydrogen bonding centres), etc.



The most recent view (see below) is that in polydental systems the intramolecular proton shift occurs mainly via a 1,2 migration.

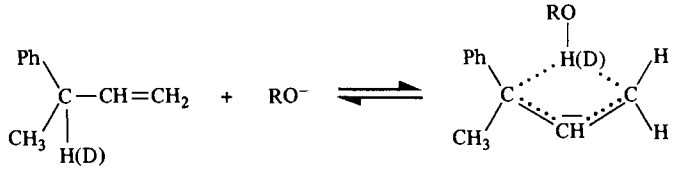
When hydrogen exchange obeys the internal return mechanism ($k_{-1}>k_2$, equation 2 in Ch. III), the protonation of an allyl anion (closed in the ion-pair) on the opposite side of the ambidental allyl system may proceed at a greater rate than does the isotope exchange. Indeed, Cram and Uyeda[523] showed that the isomerisation of 3-phenyl-butene-1 in a t-BuOD/t-BuOK system is an intramolecular process to the extent of 50%.



(prevails)

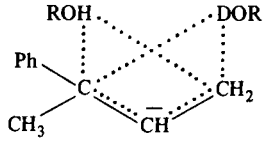
The extent of intramolecular protonation is only 17% with 3-deutero-3--phenylbutene-1 studied in a tert-butanol/potassium tert-butoxide system.

This fact, and the data obtained for other solvent/base systems, suggest that the ratio of the intramolecular to the intermolecular products depends on the starting position of the deuterium. In deuterated media the ratio is 3 to 10 times as high as it is where deuterium is in the substrate[285]. This, evidently, is due to the different abilities of hydrogen and deuterium to form hydrogen (deuterium) bonds. The intramolecular isomerisation mechanism may be represented as follows in the form of 1,3-hydrogen migration.



XXV

Alcohols (ROH) form stronger hydrogen bonds than do the deuterated species[524], therefore structure XXV is better when it includes the alcohol rather than the deuterated species. Consequently, as illustrated below, intermolecular protonation of the ambidental allyl anion via a transition state[285] should proceed with greater facility when the deuterated species is the departing group and the alcohol is the entering group, i.e., when the deuterated hydrocarbon isomerises in a non-deuterated medium.



(the ion-pair cation is omitted for simplicity)

Cram[285] and Cram and Uyeda[523] succeeded in establising a coherence between hydrogen/deuterium exchange and re-arrangement in optically active 3-phenylbutene-1. The $k_{exchange}/k_{rac}$ ratio found in a tert-butanol/potassium tert-butoxide system was above 10, that is, the isotope exchange had a high retention. In ethylene glycol/potassium ethylene glycoxide, $k_{exchange}/k_{rac}$ was 0.7 indicating that inversion is the main process.

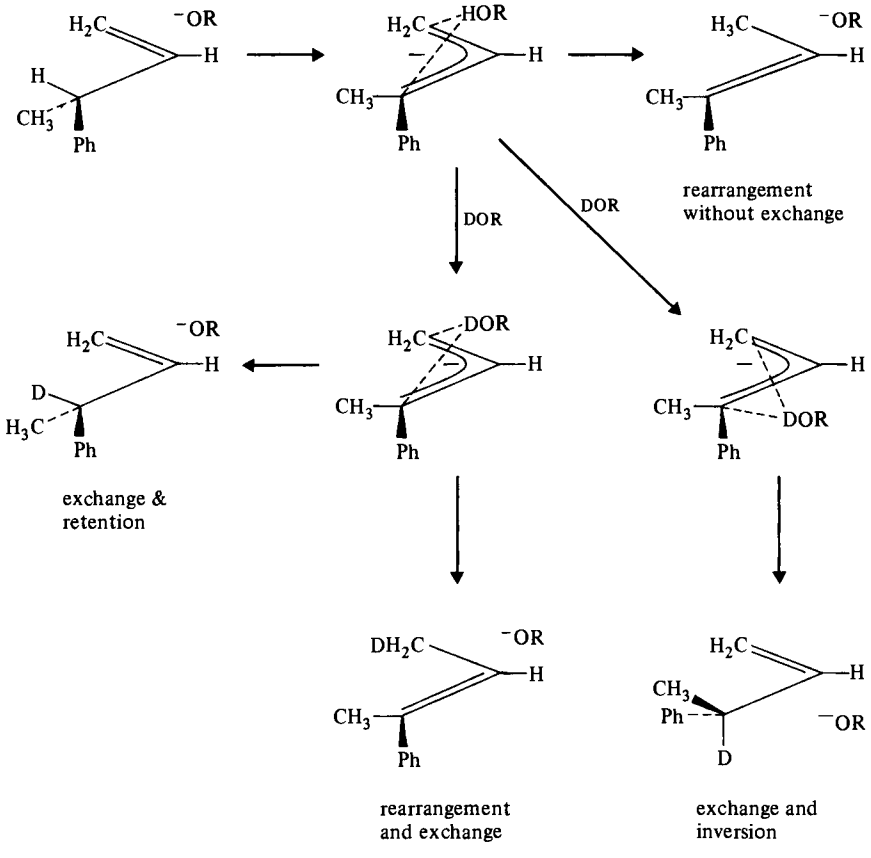
The scheme presented below includes the exchange stereochemistry and the carbanion allyl re-arrangement. It states that the base (in the form of an ion-pair , omitted in the scheme) captures a proton from the benzyl carbon resulting in a one-step formation of the carbanion hydrogen-bonded by the two poles of the ambidental system to the same hydroxyl group. The fate of this hydrogen bonded system is clear from the scheme.

If the ion-pair (K^+OH^-) (ROD) is the base-catalyst (this is the case in tert-butanol) and the metal cation participates in the transition state of C-H bond fission, then hydrogen/deuterium exchange will occur on the front side- the carbanion ion-pair intermediate collapses to give the starting compound with retainment of configuration.

The exchange process involves a sequence whereby a moiety consisting of metal cation and the ligands bonded thereto in the ion-pair rotates and the intermediate species decompose to give the starting components. In a solvent of low polarity such as tert-butanol, this process occurs faster than does the dissociation of the ion-pair.

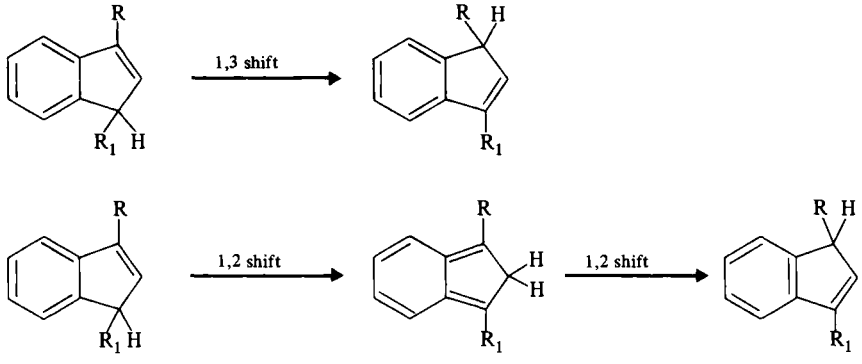
In a more polar solvent such as ethylene glycol, exchange with the solvent begins to play a role and the carbanion transforms to a deuterium-containing solvated complex whose configuration is the opposite of the starting one. The latter complex collapses to give the starting components, leading to inversion[285].

The intramolecular proton transfer applies to indene systems as well. These

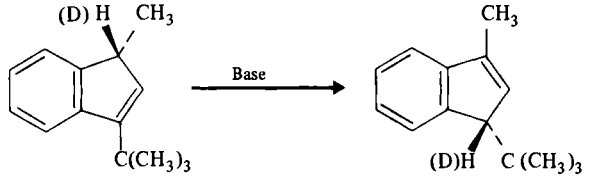


give anions with three hydrogen bonding centres (positions 1, 2, and 3), however, the bonding in position 2 is less favourable as compared with positions 1 and 3 since the isoindene structure is less favourable. A priori, it is not possible to say whether isomerisation occurs via a direct 1,3 shift or via two successive 1,2-shifts, (see overleaf).

Bergson and Weidler[525] found, however, that optically active 3-methyl-1-tert--butylindene (XXVI) gives 1-methyl-3-butylindene XXVII, the reaction being highly stereospecific (assymmetric 1,3-induction) in a pyridine/triethylamine



system. The same was found in the case of pyridine/trisopropylamine. Consequently, only one of the facets of the π-electron system takes part in proton transfer. If the reaction proceeded via two successive 1,2 shifts, stereospecificity could hardly be high since the isoindene intermediate has two equivalent hydrogen atoms.



XXVI XXVII

Mironov et al[526-528] found that 5-deuterocyclopentadiene when heated up to 60°C in the absence of a base, gave a mixture of the starting compound and 1- and 2-deuterocyclopentadienes containing no significant amounts of the non- or dideuterated compounds. This suggests that an intramolecular equilibrium process occurs in the system (/1,5/ -sigmatropic re-arrangement, in terms of the Woodward and Hoffmann notation). The re-arrangement was studied by Mironov[529], McLean[530-532] and Roth[533], extensively, and their conclusions may be summarised as follows.

(1) Re-arrangement proceeds in the liquid or gas phase under mild conditions and follows first-order kinetics. 5-Alkylated cyclopentadienes are thermodynamically less stable than are those containing the alkyl at the vinyl carbon, so they may be obtained at lower temperatures only. The 5-alkylcyclopentadiene content of the equilibrium mixtures is below 1%

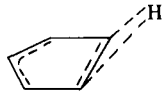
(2) The energy of activation is 20 to 25 kcal/mole, so no evidence for

exchange is expected or, indeed is found in the nuclear magnetic resonance spectrum. At higher temperatures cyclopentadiene undergoes a Diels-Alder dimerisation; if it contains substituents which would specially hinder the dimerisation exchange broadening and coalescence will be observed (e.g., triphenylmethylcyclopentadiene[534]) in the proton magnetic resonance spectra at 150 to 200°C.

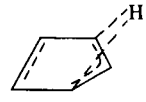
(3) Intramolecular alkyl shift may be observed in 5- and 5,5-di-substituted alkyl cyclopentadienes.

(4) The isomerisation rate increases sharply in the presence of base.

Ustynyuk[535] has calculated transition state energies for cyclopentadiene in terms of the isolated molecule approximation for three mechanisms: (2C), 1,2 shift; (3C), 1,3 shift; and (5C), an h^5 transitions complex.



2C



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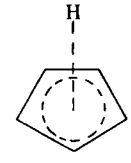


5C

TABLE 65

Calculated Differences Between Energies of Ground State (GS) and Transition States of Various Types (TS) for Intramolecular Proton Transfer in Cyclopentadiene[535]

Method	ΔE = E(GS) -E(TS), kcal/mole		
	(2C)	(3C)	(5C)
Experimental	24.5	-	-
CNDO/2	10.6	60.9	101.0
MINDO/2	18.4	-	-

Table 65 shows that (2C) is the most favourable transition state. The MINDO/2 method is in a better agreement with experiment while the ΔE value found via CNDO/2 is approximately one half of the experimental value. The transition state (2C) is characteristic in that the positive charge grows on the migrating hydrogen atom and the negative charge on the ring carbons. However, the bond of the migrating hydrogen with the C_5H_5 group remains essentially covalent. Also, the ring bond lengths are levelled as compared with the ground state.

It is possible to deduce the following ideas regarding structural changes of cyclopentadiene occuring along the reaction co-ordinates[535]. In the region of the ground state (minima) the angles between C_5-$H_{migrating}$ or C_5-$H_{non\text{-}migrating}$ and the ring plane are the most variable. Then, in the region

of "slope" of the potential energy surface, the bonding of the migrating hydrogen with the π-electron system starts increasing, the positive charge built up on the migrating hydrogen increases markedly, and negative charges on C_1 and C_3 increase. In the transition state region the ring π-orbitals, all bond lengths, and the π-bond orders are the most variable.

Intramolecular proton transfer in cycloheptatriene probably occurs in a similar way, via successive 1,2 shifts. The contribution by intramolecular protonation depends on the solvent/base system applied. Doering and Gaspar[536] who studied 1, 1-dideuterocycloheptatriene in a dimethylsulphoxide/triethylcarbinol/potassium triethylcarbinol system found that isotope exchange and isomerisation involve only a negligible intramolecular protonation, whereas in a triethylcarbinol/potassium triethylcarbinol system, intramolecular protonation is 12 times as fast. This may be due to the polarity of the medium. Possibly, free carbanions play the role in dimethylsulphoxide, whereas ion-pairs play the role in triethylcarbinol.

In Chapter III is discussed the part played by intramolecular proton transfer in converting the quinoid III into the triarylmethane IV. Formally, it was assumed that a 1,5 proton shift was involved; a more probable assumption is a succession of two 1,3 shifts[285]. The intramolecular/intermolecular rates ratio in this system also depends on the polarity of the medium, and intermolecular protonation prevails in polar ethylene glycol whereas intramolecular protonation does so in tri-ethyl-carbinol. The effects of solvent and base on the rates ratio have been discussed in detail by Cram[285].

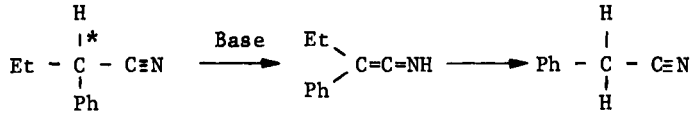
Intramolecular proton transfer has also been observed in the isomerisation of Schiff bases[537], in acetylene-allene re-arrangements[538] and in the racemisation of nitriles[500], showing that intramolecular proton transfer is a widespread phenomenon, especially in media of low polarity where the ion-exchange mechanism predominates.

$$R_2CH - N{=}CR_2' \xrightarrow[ROD]{RO^-} R_2C{=}N - \underset{(D)}{CHR_2'}$$

acetylene-allene re-arrangements,

$$Ar - CH_2 - C{\equiv}C - Ar \xrightarrow{Base} Ar - CH = C = CH - Ar$$

and nitrile racemisation



optically active racemate

2. Effects of Structure upon the Isomerisation of Allyl Systems

Schreisheim and Rowe[539,540] have studied the rates of isomerisation of alkenes-1 in dimethylsulphoxide/potassium tert-butoxide. The degree of isomerisation was maintained at about 30-50% so that the composition of products should correspond to kinetic rather than to thermodynamic control. The system dimethylsulphoxide-potassium tert-butoxide is a fairly ionising solvent, therefore, the isomerisation may be thought of as predominantly intermolecular. Olefines of four types were studied by Schriesheim and Rowe,

CH_2=CH-CH_2R, CH_2=C(CH_3)-CH_2R, CH_2=CH-CH(CH_3)R, and CH_2=CR-CH-CH_3 (R was alkyl, phenyl or vinyl). The effect of the substituent R upon the relative isomerisation rate was found to be identical in all these four olefine types, the maximal reactivity difference for a series being about 10^7. The accelerating effects of substituents may be arranged as follows.

$$CH_2=CH>Ph>H>Me>Et>n\text{-}Pr>iso\text{-}Pr>tert\text{-}Bu$$

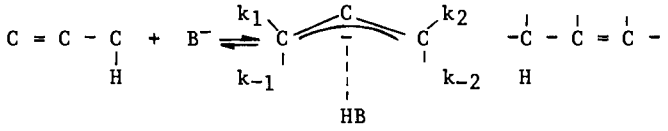
On the whole, the series obeys the Taft equation although the last two compounds react slower than they should have reacted based on their Taft σ constants, with the deviation being much higher for the tert-butyl compared with the isopropyl compound. This may be due to spatial hindrances to the formation of the planar transition state[285].

Schreisheim et al[541] also studied isomerisation of methylene cycloalkanes in a dimethylsulphoxide/potassium tert-butoxide system

(n = 3.7)

The highest rate was observed for methylenecyclobutane, the lowest rate for methylenecyclohexane. If it is assumed that the three allyl carbons tend towards a planar transition state, then, the higher rate found for methylenecyclobutane may be explained by the fact that the non-bonded H-H interaction of the neighbouring methylenes disappears from the planar carbanion. The simultaneous increase in the angular strain evidently plays no significant role.

Kinetic data on olefine isomerisations are often hard to interpret in detail since proton abstraction leading to the carbanion is a reversible process. With the "intramolecular internal return mechanism" ($k_{-1}>k_2$, see equation below), the carbanion intermediate transforms to the final (k_2) and the starting (k_{-1}) species, so k_2/k_{-1} can be obtained. However, neither k_{-1} nor k_2 are usually known, so a conventional assumption is that either $k_2>k_{-1}$ or $k_2(k_{-1} + k_2)$ = constant for the systems to be compared



The rule proposed by Ingold[542] often helps to predict which of the constants, k_{-1} or k_2, is higher. It states that in the protonation of a mesomeric anion, the thermodynamically less stable tautomer is formed faster. The same tautomer more easily loses a proton under the action of bases. The rule is applicable to numerous systems such as the base catalysed isomerisation of olefines with terminal double bond, allyl alkyl ethers, N,N-dimethylallylamine, and of other compounds. Such isomerisation gives rise initially to the less stable cis-isomers which, at more prolonged reaction times, are transformed to the trans-isomers (see references in Chapter V[285]). Similarly, aci-nitroalkane salts when neutralised by acid give unstable aci-nitro compounds which then gradually transform to give the nitroalkanes[542].

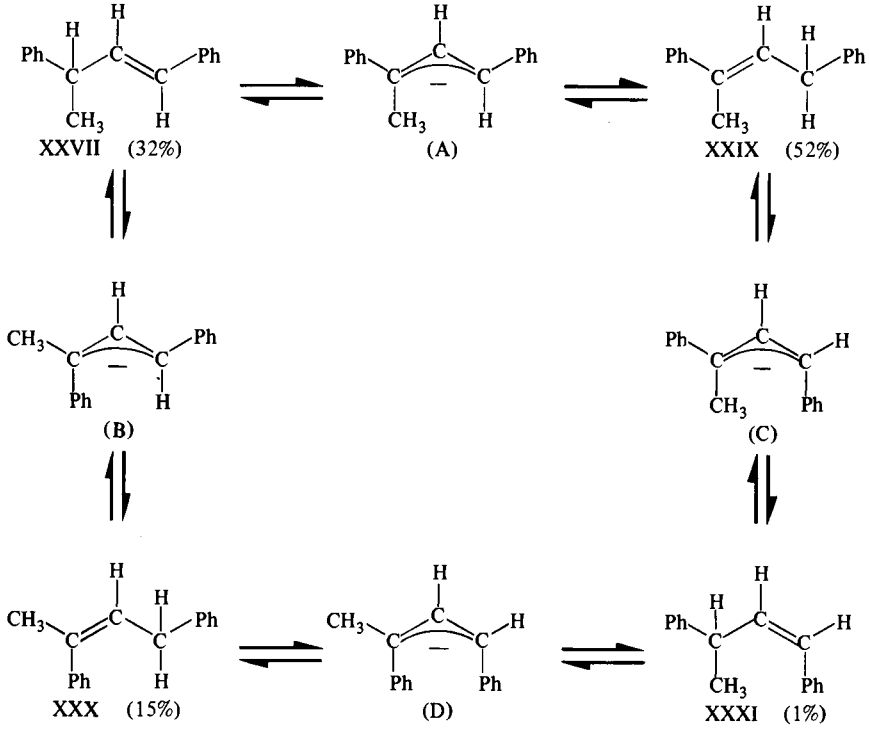
One explanation of such reactions is that the preferential formation of

thermodynamically less stable isomers under kinetic control conditions might be explicable by assuming that the reacting olefine is in the conformation whose β-carbon is in the cisoid position to the double bond. This makes the hydrogens attached to the β-carbon interact with the double bond π-electrons, which should[543] favour the process.

An alternative explanation resolves essentially into estimating the equilibrium between the eclipsing effect upon, and the spatial hindrance to, solvation of the transition state[285].

Interconversions of four isomeric 1,3-diphenylbutenes XXVIII - XXXI show that the lower stability preference rule discussed above is in some cases violated[544]. The energy of formation of the allyl anion may be lower for the more stable isomer as compared with the less stable one.

When acted upon by potassium tert-butoxide in tert-butanol at 40°C these four olefines give the following equilibrium mixture.



The isomerisation rate constants and (for the t-BuOD medium) the ratios of isotope exchange rate constant to the isomerisation rate constant are listed below.

	k_{isom}, M^{-1} sec^{-1}	$k_{exchange}/k_{isom}$
XXVIII	$5.1\ 10^{-5}$	below 0.3
XXIX	$3.2\ 10^{-5}$	17
XXX	$1.8\ 10^{-6}$	21
XXXI	$7.5\ 10^{-8}$	below 0.07

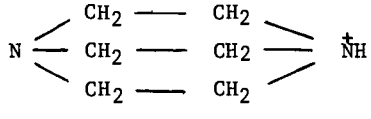
To explain the XXVIII ⇌ XXIX interconversion and, on the other hand, the XXVIII ⇌ XXXI interconversion, two isomeric allyl anion, (A) and (B), should be introduced. The energy barrier of the conversion (A)→ (B) is 3 kcal/mole at 40°C[371]. The 1,3 steric repulsion of the substituents makes the carbanions (C) and (D) less stable, so the isomerisation rate of compound XXX is low.

Isotope exchange in the benzyl position of compounds XXXI and XXX is faster than is their isomerisation leading to compound XXVIII. Consequently, protonation of the anion (A) yields compound XXIX faster than it yields compound XXVIII. Similarly, the protonation (B)→ XXX is faster than is (B)→ XXVIII. These observations have been assigned to the inductive effect of the methyl group favouring protonation of a less substituted side of the carbanion. In other words, the anions (A) and (B) are protonated more rapidly in the position the saturation of which leads to a more thermodynamically stable isomer.

3. Effects of the Medium

The effects of the solvent medium on allylic re-arrangements have been studied by Cram et al[545-547] in the case of 1-methyl-3-tert-butylindene XXVII. He found that XXVI ⇌ XXVII equilibrium rate constant measured in tert-butanol was K_{eq} = 7.4[547], that is, the isomer with the methyl group at the double bond is more stable owing, probably, to hyperconjugation. The XXVI ⇌ XXVII forward and inverse rate constants are 8.8×10^{-4} and 1.2×10^{-4} sec^{-1}, respectively. The optically active compound XXVIII was of assistance in enabling simultaneous measurements to be made of the rates of isomerisation (k_i), deuterium exchange ($k_{exchange}$), and racemisation (k_{rac}).

In t-BuOD, the k_i/k_{rac} ratio is strongly dependent on the base catalyst used. With pentamethylguanidine, the process of capture of a proton to form a cation with a delocalised charge has a value of k_i/k_{rac} 24 to 53 depending on the base concentration. With triethylene diamine, however, in whose cation there is no charge delocalisation, k_i/k_{rac} is 40,000



This large difference in k_i/k_{rac} ratio is due to the different ion-pair structures involved. The suprafacial base catalysed isomerisation in the structurated ion-pair follows[547] the conducted tour mechanism. The amine leads the proton along the π-facet of the anion from position 1 to position 3 where the system collapses to its covalent state. The cation in the

structurated ion-pair is hydrogen-bonded with the hydrogen bond spearheads of the anion. The proton motion along the π-facet may be a direct 1,3 shift, although a succession of 1,2 shifts cannot be ruled out. A mechanism of the type is, of course, more likely to be involved in the case of triethylene diamine.

Antarafacial racemisation, which is a slower process, follows the isoinversion mechanism involving a relatively non-structurated ion-pair whose energy is higher than that of the structurated ion-pair in the conducted tour mechanism. Non-structurated ion-pairs are more likely to occur in the case of pentamethylguanidine; that is why the k_i/k_{rac} value observed with pentamethylguanidine is 80 to 160 times higher than, i.e., the racemisation is 80 to 160 times as fast as, that observed in the case of triethylene diamine.

An increase in racemisation has also been observed on adding crown ethers. In MeOD/MeOK and in MeOH/MeOK, isomerisation results in complete racemisation; the product containing 97% deuterium. Thus, the contribution of intramolecular proton transfer in this mechanism is 13%. In methanol, the $k_{exchange}/k_{rac}$ ratio is about unity. This is due to high polarity of the medium and, consequently, the higher probability of dissociation of an ion-pair to free ions. In this case, the addition of a crown ether is, as expected, not effective at all. However, in an non-polar medium such as benzene (75%) /phenol (25%)/potassium phenoxide the $k_{exchange}/k_{rac}$ ratio is 8 in the absence of a crown ether and decreases to 2 in the presence of a crown ether. The crown ether makes the ion-pair less structurated and thus hinders operation of the conducted tour mechanism. This agrees with the fact that the isomerisation rate of 3-methyl-1-tertbutylindene (XXVI) is almost ten times as low in the presence of a crown ether[546].

Chapter V

Relationship Between Equilibrium and Kinetic Acidity

In a consideration of a series of equilibria between different acids HA and one and the same base B, (equation 1) a natural assumption would be that the proton abstraction rate k_f would decrease with an increase in pKa (HA) (or more precisely with a decrease in $\Delta pKa = pk(HB) - pK(HA)$).

$$HA + B \underset{k_g}{\overset{k_f}{\rightleftharpoons}} A + HB \qquad (1)$$

Consequently, it might be anticipated that a correlation exists between equilibrium and kinetic acidities, agreeing with the parallelism observed between lgk_f and pKa in various series of related compounds.

In some cases, however, the situation is just the opposite with an increase in equilibrium acidity leading to a decrease in the proton abstraction rate. An example of this is provided by the nitroalkanes. Equilibrium acidity increases, and kinetic acidity decreases along the series CH_3NO_2, $C_2H_5NO_2$, $(CH_3)_2CHNO_2$.

In the nitroalkane series, the protophilic proton abstraction mechanism does not seem to be affected on going from one nitroalkane to another in the series. On the other hand, as has already been mentioned, (Chapter III) the proton transfer mechanism involved may differ if a wide range of CH-acid structures is considered, thus the protophilic mechanism may give way to the addition-elimination mechanism (in aromatic hydrocarbons) or to the electron transfer mechanism (with polynuclear aromatics).

Even when the protophilic mechanism does apply to a series of CH-acids the experimental hydrogen exchange rates might not reflect the intrinsic kinetic acidity since the internal return mechanism may interfere in the process.

Consequently, a careful analysis is necessary of the effects of structure upon kinetics, mechanism, kinetic isotope effects, Brönsted factors, etc. If this is not done, then hydrogen isotope exchange data can hardly be expected to serve as a measure of relative CH-acidity or of the relative stability of carbanions.

The correlations between equilibrium and kinetic acidities are based on the Brönsted equation[278]. This equation constitutes the main subject of this Chapter, with the emphasis being put on the whys and the wherefores of deviations from dependence on the equation.

I. THREE-STEP PROTON TRANSFER MECHANISM

It is conventional to assume that the reaction represented in equation 1 includes, at least, three kinetical steps[16,548,549], written below. In Chapter III steps (1) and (2) are combined for purposes of simplicity.

$$AH + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (AH\cdots B) \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (A\cdots HB) \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A + HB \quad (2)$$

Steps k_1 and k_{-1} refer to the formation and the decomposition of the primary encounter complex AH···B, and steps k_2 and k_{-2} correspond to proton transfer in the complex, whilst steps k_3 and k_{-3} correspond to the decomposition and the formation of the secondary encounter complex A···HB. The base and the acid in the encounter complexes interact via hydrogen bonding, therefore, they may be also called hydrogen-bonded complexes.

Under steady-state conditions with respect to both the hydrogen-bonded complexes, AH···B and A···HB, the forward reaction rate constant (k_f) may be written as follows.

$$k_f = \frac{k_1 k_2 k_3}{k_{-1}k_3 + k_2 k_3 + k_{-1}k_{-2}} \quad (3)$$

Generally speaking, any of the steps in equation 2 may be rate-determining.

When $k_2 >> k_{-1}$ and K_2 (i.e. $k_2/k_{-2}) >> k_{-1}$, then $k_f \cong k_1$ and the limiting step is the formation of the hydrogen-bonded complex from the initial species.

When $k_2 << k_{-1}$ and $k_3 >> k_{-2}$, then $k_f \cong K_1 k_2$ (where $K_1 = k_1/k_{-1}$) and the rate is controlled by the rate of proton transfer within the impact complex.

When $k_{-2} >> k_3$ and $k_{-1} >> K_2 k_3$, then $k_f \cong K_1 K_2 k_3$ and the rate is controlled by the decomposition of the secondary complex to reaction products.

When K_1 is very high, the steady-state conditions will be satisfied only at very low concentrations.

TABLE 66

Equilibrium Constants for the Following Reaction in Acetonitrile[550,551].

$$AH + A^- \rightleftharpoons HA_2^-$$

AH	A^-	$K_1 (M^{-1})$
HBr	Br^-	2.5×10^2
HCl	Cl^-	1.6×10^2
PhCOOH	$PhCOO^-$	4×10^3
PhOH	PhO^-	6×10^5
NH_4^+	NH_3	10
$CH_3NH_3^+$	CH_3NH_2	30
H_2SO_4	HSO_4^-	10^3

The existence of primary hydrogen-bonded complexes is beyond doubt. An example is given by the homoconjugates HA_2^- of HHal-. OH-, or NH-acids. Homoconjugation constants measured for some acid/base pairs in acetonitrile are listed in Table 66. The data for ROH/RO^- in dimethylsulphoxide are discussed in Chapter I.

If it is assumed that K_1 is about 10^5 M^{-1}, (k_1 may be of the order of 10^{11} M^{-1} sec^{-1},[552] then an estimate for k_{-1} will be of about 10^6 sec^{-1}. Thus, k_2 should be less than 10^6 sec^{-1} for the proton transfer to be rate-controlling[16].

With CH-acids, there is good spectroscopic evidence for the existence of hydrogen-bonded complexes of O-bases with telatively acidic compounds such as chloroform, acetylenes, aldehydes, fluorene, and others.[524]

The existence of the secondary complexes (A···HB, equation 2) follows from the fact that CH-acids often racemise and isomerise in the absence of any hydrogen exchange with the solvent. This has been discussed in Chapter IV.

The free energy of proton transfer, (Q), corresponds to the difference between the pKa values of the acid and of the base. The Brönsted relation states essentially that the change in the energy of activation ($q^{\neq}$) of the proton transfer is proportional to the change in the standard free energy of the reaction, (equation 4).

$$\alpha = \frac{\partial q^{\neq}}{\partial Q} = \frac{\partial \lg k_f}{\partial \Delta pK_a} \qquad (4)$$

where α is the proportionality factor and $\Delta pKa = pK_a(HB) - pKa(HA)$.

Combining equations (3) and (4) gives the following relationship

$$\alpha = \frac{k_{-1}k_3}{k_{-1}k_3 + k_2k_3 + k_{-1}k_{-2}}\,\alpha' + \frac{k_{-1}k_{-2}}{k_{-1}k_3 + k_2k_3 + k_{-1}k_{-2}},$$

where $\alpha' = \partial \lg k_2 / \partial \Delta pKa$ is the proportionality factor between pKa and the logarithmic rate constant of the proton transfer proper in the encounter complex.

Similar equations may be written for the inverse reactions as follows,

$$\beta = -\frac{\partial \lg k_b}{\partial \Delta pKa} = \frac{k_{-1}k_3}{k_{-1}k_3 + k_2k_3 + k_1k_{-2}}\,\beta' + \frac{k_2k_3}{k_{-1}k_3 + k_2k_3 + k_{-1}k_{-2}}$$

where $\beta' = -\partial \lg k_{-2} / \partial \Delta pKa$.

When the forward and the inverse reactions proceed via the same transition state then $\partial \lg k_2 = -\partial \lg k_{-2}$, and the above equations for α' and β' give $\alpha' + \beta' = 1$.

When $\Delta pKa = pK_a(BH) - pK_a(AH)$ is very high, then $k_2 >> k_{-1}$, $K_2 >> k_{-1}$, and hence $\alpha' \simeq 0$. When the proton transfer is very fast, consequently, the reaction is independent of ΔpKa. It is diffusion-controlled, being governed by the rate of formation of the encounter complex.

When $k_3 << k_{-2}$ and $k_{-2} >> k_2$ (the situation when HA is markedly less acidic than HB), then $\alpha' \simeq 1$. Thus, when proton transfer is slow the reaction rate is maximally sensitive to change in ΔpKa. Since $\alpha' + \beta' = 1$, $\beta' = 0$ at $\alpha' = 1$, and $\beta' = 1$ at $\alpha' = 0$

It can be easily shown that $\alpha \simeq \alpha'$ and $\beta \simeq \beta'$ when the proton transfer proper controls the reaction, i.e. when $k_2 >> k_{-1}$ and $k_3 >> k_{-2}$.

Consequently, plots of logarithmic proton transfer rate constant versus ΔpKa for the forward reaction.

$$\lg k_f = \alpha \cdot \Delta pKa + \text{const.} \qquad (5)$$

and for the inverse reaction

$$\lg k_b = -\beta \cdot \Delta pKa + \text{const.} \qquad (6)$$

should contain three regions with different α and β values (Fig. 15) (i) When ΔpKa>>0, α = 0 (β = 1); (ii) when ΔpKa<<0, α = 1 (β = 0) and (iii) when the pKa values of HA and HB are close to each other, we have the transient region, 0<α<1.

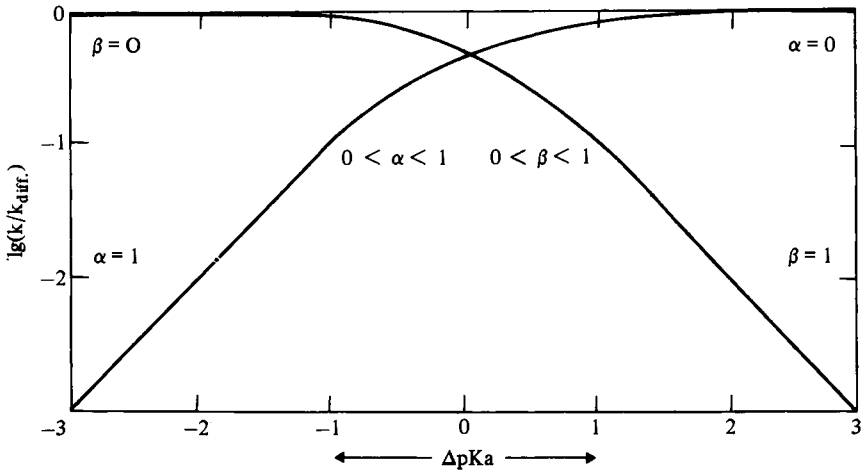


Fig. 15 Theoretical plot of lgk vs. ΔpKa; k_{diff} is the diffusion rate constant (See ref. 16).

The explanation given above for the limiting α and β values close to zero or unity is based on diffusion limitations of the forward and inverse reactions. This model was proposed for the first time by Eigen[16]. Such a model may be valid for fast reaction such as the proton transfer or protons from hydroxy acids to O-bases in aqueous solutions. With slow reactions, however, an alternative explanation of the α and β patterns is possible. This is based on the concept of energy curves of the reactants and the reaction products and is discussed further in the next Section.

Equations (5) and (6) are the Brönsted equations for the forward and inverse reactions. The Brönsted plots are characterised by three parameters: (i) the limiting values of $\lg k_f$ at α= 0 and of $\lg k_b$ at β = 0, (ii) the slopes at the transient region, especially at ΔpKa = 0, and (iii) the absolute values of $\lg k_f$ (equal to $\lg k_b$) at ΔpKa = 0. Factors (i) and (ii) govern the symmetry of the α- and β-curves vis-a-vis the point ΔpKa = 0, and factor (iii) reflects the width of the region ΔpKa in which α and β vary from 0 to 1.

II. THEORETICAL INTERPRETATION OF THE BRÖNSTED EQUATION

In 1924, Brönsted and Pedersen[278] on the basis of measurements of the catalysed decomposition rates of nitramide found that the rate constants (k_B) and the basicity constants (K_B) are interrelated as follows.

$$k_B = 6.2 \times 10^{-5} K_B^{0.83}$$

Since then, many similar correlations for other reactions involving proton transfer have been obtained. The Brönsted equation is, essentially, an expression of the principle of the linearity of free energy, an expression that appeared more than ten years ahead of the well-known Hammett equation.

It is noteworthy, however, that the first empirical relation of the Brönsted type was proposed by Tafel as early as 1905. He interrelated the hydrogen overvoltage during the cathodic reduction of the hydroxonium ion (H_3O^+) (η; a thermodynamical factor) with the logarithmic current density (lgi, a kinetic factor); this expression is know as the Tafel formula[553].

$$\eta = \alpha + b \lg i$$

More recently it was shown that $b = RT/\alpha n_a F$ where α is the electrochemical transfer coefficient similar to the Brönsted coefficient α , and RT/n_aF (equal to 60 mV at 25°C and $n_a = 1$) converts lgi into electrochemical units. The η and (RT/n_aF)lgi terms of the Tafel formla are equivalent to ΔpKa and $\lg k_f$ terms respectively, in the Brönsted equation. Development of the concept of electrochemical transfer coefficient is closely paralleled by the development of the concept of the Brönsted coefficient. The physical meaning of the transfer coefficient has been critically reviewed by Bauer[553]. Recent developments in the Brönsted relationships has been discussed by Kresge[554].

In their original paper, Brönsted and Pedersen[278] predicted that, in general, plots of $\lg k_f$ and $\lg k_b$ versus ΔpKa should form non-linear rather than straight line relationships. They predicted, also, that α has a value of unity at strongly negative ΔpKa and also that α is zero at strongly positive ΔpKa, and that α varies from unity to zero in the transient region.

Theoretical interpretation of change in the Brönsted coefficient when the process not controlled by diffusion is often based on the energy curves concept. Consider the proton transfer proper in an encounter complex, viz., the case when the same base abstracts protons from different acids. Horiuti and Polanyi[555] proposed that a variation in the structure of the acid AH (e.g. introduction of substituents) leads to a vertical shift in the potential energy curve, as shown in Fig. 16, without affecting the shape of the curves and the position of the minimum on the reaction co-ordinate. The plot in Fig. 16 shows that if the branches of the parabola are approximated to by straight lines, then the following relationship applies,

$$\alpha = \frac{\Delta q^{\neq}}{\Delta Q} = \frac{\operatorname{tg}\theta}{\operatorname{tg}\theta + \operatorname{tg}\vartheta}$$

Consequently, α is governed by the slopes of the energy curves at the intersection. Horiuti and Polanyi found that if α = 0.5 then the AH···B and A···HB slopes are equal in the vicinity of the intersection.

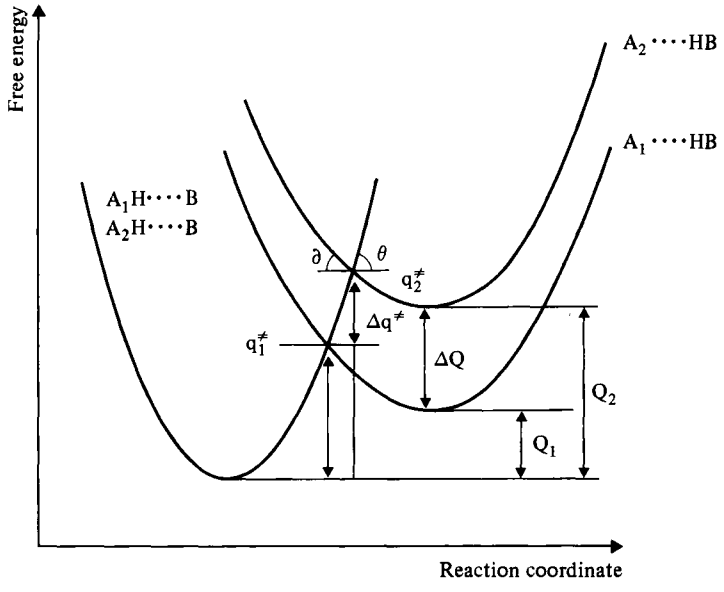


Fig. 16. Theoretical interpretation of Brönsted exponent (see text)

The most exothermic reactions correspond to the intersection lying at the apex of the AH···B parabola (Fig. 17). In this case the reactants "roll down" from the well AH···B to the well A···HB. In other words, the proton is transferred spontaneously and the energy of activation is zero. Reactions of this type are called non-activational reactions (α = 0). It is very difficult to make a non-activational reaction occur since formation of an encounter complex or decomposition may become the limiting step at very high proton transfer rates. Thus, values of α of zero result from diffusion control rather than control by the intersection mode.

The most endothermic reactions correspond to the energy curves crossing at the apex of the A···HB parabola (Fig. 17). The highest energy corresponds to the reaction product, in other words, the reactant transforms to the product by gradually climbing up the descent of the potential energy surface and the well A···HB is, in fact, the highest point of the surface. Reactions of this kind are called non-barrier reactions (α = 1). Non-barrier electron transfer was discovered by Krishtalik[556]; as in the case of proton transfer reactions, non-barrier reactions might be anticipated to occur in the case of very slow reactions such as the reaction of very weak CH-acids with very weak bases.

In the transient region (see "normal" reaction, Fig. 17), the proton is

transferred by overcoming the energy barrier, the height of which depends on how exothermic the reaction is, and varies between zero and unity.

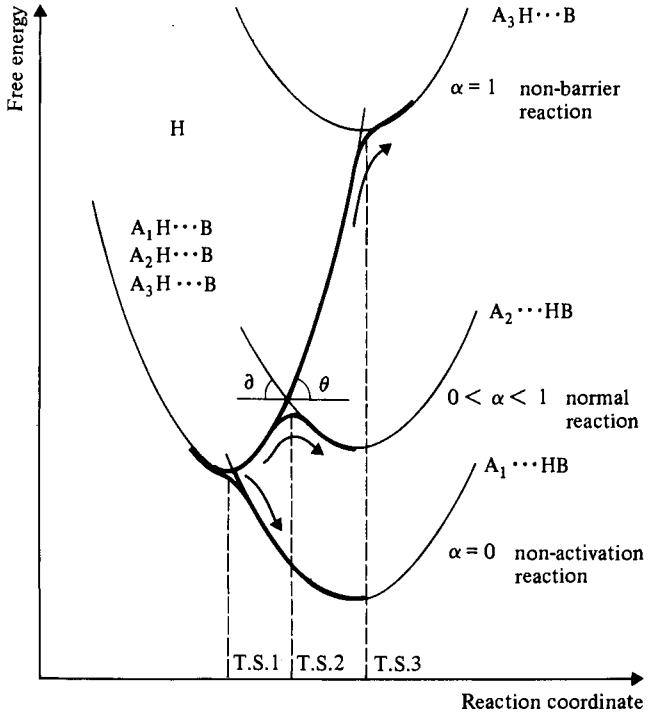


Fig. 17. Theoretical plots for non-activation, non-barrier and "normal"proton transfer

In Fig. 17 it is shown that the position of the transition state on the reaction co-ordinate depends on the pKa value of the acid (when the base, B, is kept the same). The non-activation transition state coincides with the initial complex AH...B. The non-barrier transition state is structured as A···H···B, an intermediate between AH···B and A···HB.

Thus, α varies from zero to unity in going from the non-activation to the non-barrier transition state, therefore, α may be thought of as a criterion for transition state structure. The closer α is to unity the more similar will the transition state be to the product, the closer α is to zero the more similar will the transition state be to the reactant. However, this does not necessarily imply that when $\alpha = 0.5$ the transition state is a symmetrically structured intermediate between that of the reactant and of the product. This

is so only when the proton is transferred from an acid to its conjugate base (AH···A ⟶ A···HA) because only under this condition are the AH···B and A···HB energy curves of identical shape ($tg\theta = tg\delta$, therefore α is 0.5, exactly at the half-distance between the minima). Usually, however, proton transfer products differ from the starting compounds, so the energy barrier may well be asymmetric and an α value of 0.5 will not lie at the half-distance between the minima on the reaction co-ordinate. Consequently, α describes the height of the energy barrier as a function of ΔpKa, not the symmetry of the barrier.

The interrelation between α and reactivity finds an explanation within the framework of the semi-quantitative Marcus theory[557-559] in which the free energy of activation ($q^{\neq}$) of proton transfer is related with the standard free energy (Q) by a so-called intrinsic activation barruer, $q_o^{\neq}$. The Marcus' theory was initially proposed for explaining electron transfer phenomena and later extended by him to proton transfer.

$$q^{\neq} = (1 - \frac{Q}{4q_o^{\neq}})^2 q_o^{\neq} \quad \text{at} \quad -4q_o^{\neq} \leqslant Q \leqslant 4q_o^{\neq} \tag{7}$$

The intrinsic barrier corresponds to the energy of activation when the standard free energy is zero, that is when pKa(HA) = pKa(HB). It is governed [557-559] by the structure and the re-organisation energy of the solvent, which is decisive in controlling α at zero to unity for slow proton transfer processes when the reaction rate is not yet under diffusion control.

Equations (8) and (9) are derived from equations (4) and (7).

$$\alpha = \frac{\partial q^{\neq}}{\partial Q} = \frac{1}{2}(1 + \frac{Q}{4q_o^{\neq}}) \tag{8}$$

and

$$\frac{d\alpha}{dQ} = \frac{1}{8q_o^{\neq}} \tag{9}$$

These relations demonstrate that when the intrinsic energy barrier is not high as in the case of fast proton transfer reactions the $d\alpha/dQ$ value is high, i.e. the Brönsted plot is pronouncedly curcilinear; whereas when $q_o^{\neq}$ is high the plot is smoother and the transition from an α value of unity to zero is prolonged. Thus Kresge[554] and Murdoch[549] have calculated that when $q_o^{\neq} = 1$ kcal/mole then α varies from unity to zero in a region of 4 pKa units (at $\Delta pKa = -2$ to $\Delta pKa = +2$). The intrinsic barrier of 1 kcal/mole is, of course, very low; it corresponds to a k_f of 10^{12} M^{-1} sec^{-1} for a thermoneutral process at 25°C, i.e., to reaction controlled by the formation rate of the encounter complex, this control being typical of proton transfer between hydroxy acids and oxygen bases.

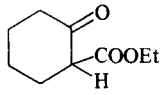
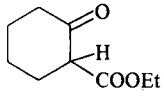
When $q_o^{\neq} = 5$ kcal/mole then α varies from zero to unity in a 12 pKa units region, when $q_o^{\neq}$ is 10 or 20 kcal/mole the region is 55 and 110 pka units, respectively. In the latter cases, the experimentally determined Brönsted plot will take the form of a straight line.

Higher values of re-organisation factors, and, respectively, lower proton transfer rates are characteristic of CH-acids (see Table 67); the

intrinsic activation energy ($q_o^{\neq}$) values in Table 67 were calculated using equation (7); the experimental heat of reaction being assumed to be equal to the free energy of the proton transfer proper, that is, the three-step nature of the mechanism was neglected. Therefore, the $q_o^{\neq}$ values listed are estimates; they are sums of the structure re-organisation energy and the solvent re-organisation energy.

TABLE 67

Re-organisation Factors for Proton Transfer Reactions in Aqueous Solutions[558] (equation 7).

AH	B	Intrinsic activation Barrier $q_o^{\neq}$. kcal/mole
RNH_3^+	RCO_2^-, ArO^-	4
$RR'R''NH^+$	$HO(CH_2)_2S^-$	5.5
NO_2NH_2	RCO_2^-, OH^-, RNH_2	6
	RCO_2^-	8.5
$CH_3COCHRR'$	RCO_2^-, ArO^-	11.5
NO_2CH_2COOEt	RCO_2^-	13
$(CH_3O)_3C_6H_4^+$	RCO_2^-, OH^-, H_2O	14
$CH_3COCHRR'$	OH^-, SH^-	13
	RCO_2^-	14.5

Next, it is possible to find which of the energies is more important. The experimental free energies of reaction (Q_{obs}) are sums of three terms (three-step mechanism, equation 2)[562], where Q is the standard free energy w^r is the heat of formation of the secondary encounter complex, and wP is the energy of formation of the secondary encounter complex.

$$Q_{obs} = Q + w^r - w^p$$

The observed free energy of activation, $q_{obs}^{\neq}$ is equal to w^r plus $q^{\neq}$ ($q^{\neq}$ is the proton transfer activation energy calculated from equation 7). Consequently, in Marcus' terms, the free energy of activation observed for the three-step process is as follows.

$$q_{obs}^{\neq} = w^r + 1 + [(Q_{obs} - w^r + w^p)/4q_o^{\neq}]^2 q_o^{\neq} \qquad (10)$$

TABLE 68

Calculated Values of $q_o^{\neq}$, w^r and w^p, kcal/mole (Assumed to be Invariable over a Reaction Series).

	Reaction	$q_o^{\neq}$	w^r	w^p	Ref. No.
1.	RCO_2H or $\bar{A}\bar{R}OH + CHN_2CO_2^- \longrightarrow$ RCO_2^- or $ArO^- + C^+H_2\bar{N}_2C\bar{O}_2^-$	5	8	-	560
2.	$R_3NH^+ + CHN_2CO_2^- \longrightarrow R_3N +$ $+ C^+H_2N_2CO_2^-$	1	14	-	561
3.	$H_3O^+ + HAr \longrightarrow H_2O + H_2Ar^+$	10	10	8	165
4.	$RCO_2H + CH_2CN_2COCH_3 \longrightarrow$ $RCO_2^- + CH_3C^+HN_2COCH_3$	2	16	-	562
5.	$RCO_2H + CH_3CN_2COOEt \longrightarrow$ $RCO_2^- + CH_3C^+HN_2COOEt$	2	14	-	562
6.	O-Bases + $CH_3COCH_2COCH_3 \longrightarrow$ OH-acids + $CH_3COC^-HCOCH_3$	3	11	9	561, 563
7.	RCO_2^-(pKa 4) + ketones $\longrightarrow$ RCO_2H + enolate anions	3	14	7	87, 562.

Calculations made with the aid of equation 10 are given in Table 68. The Table lists mainly reactions involving the protonation of carbon-bases such as diazoacid anions or aromatic hydrocarbons. Their CH-acids are positively charges (Reactions 1-5, Table 68). Two of the reactions (nos. 6 and 7, Table 68) involve the ionisation of neutral CH-acids under the action of oxygen--bases. Reaction 8 is an acid-catalysed dehydration of acetaldehyde hydrate.

The data in Table 68 shows that the intrinsic energy barrier is generally speaking, markedly lower than is the heat of formation of the primary encounter complex. On average, w^r is about 11 kcal/mole; which is much higher than is the energy necessary for localising the base next to the acid (the latter energy is RTln55.5, ca.2.5 kcal/mole, in aqueous solution). Kreevoy et al[560,561] assumed that the remaining energy is required for transforming the encounter complex to the reaction complex. This would require the re-organisation of the solvent shell of the reactants by, e.g., removing a molecule of water that solvates the base, so that an acid molecule could take the place of water. Indeed, proton transfer between CH-Acids and oxygen-bases in water implies direct contact, without water molecules being inserted between the base and the acid[560], so the oxygen-base should be desolvated for the reaction to proceed. It is highly probably that the main contribution in w^r (and w^p) is made by the solvent re-organisation energy[548]. Consequently, the reactions of CH-acids with oxygen-bases and of carbon-bases with hydroxy acids listed in Table 68 are more sensitive to the solvent re-organisation. Only in the case of the reaction of arenes with perchloric acid in water (No. 3,Table 68), is the intrinsic barrier sufficiently high (10 kcal/mole), owing to the loss of aromaticity during protonation of the arene.

In reactions of hydroxy-acids with oxygen-bases, desolvation should

contribute to a smaller extent because the desolvation energy is markedly compensated for by the formation energy of the O···HO bond in the acid/base encounter complex. A high w^r value (13 kcal/mole) as found by Kresge[554] for the acid-catalysed dehydration of acetaldehyde hydrate ($CH_3CH(OH)_2$) can be explained by assuming a contribution of the cyclic transition state involving the three molecules, acetaldehydehydrate,acid and water.[564]

The prevailing role played by solvent re-organisation, especially in hydroxyl-containing solvents, has been clarified by the large amount of theoretical and experimental work that has been carried out, as will be considered in this and the ensuing Sections.

Theory predicts three possible mechanisms for the proton transfer proper: a coupled mechanism and two three-step mechanisms[565]. The coupled mechanism operates when a proton is transferred from an acid to a small base; proton transfer is concerted with solvent re-organisation. With bulky bases, a three-step mechanism may operate consisting of (i) solvent re-organisation, (ii) proton transfer, and (iii) solvent relaxation leading to the products, these steps proceeding in succession. A further three-step mechanism proposed for bases of intermediate sizes presumes that the solvent configuration is not at equilibrium with the transition state structure. This latter mechanism is believed to be most uncommon[565].

Ritchie and Ushold[97,286,356,566] applied the stopped-flow techniques[350] to the measurement of fast proton transfers from CH-acids to carbon- or oxygen-bases in dimethylsulphoxide and methanol. The Brönsted plots were non-linear (Streitwieser pKa's used). The proton transfer rate was found to be markedly lower in methanol than in dimethylsulphoxide, even when allowance was made for the changes in basicity on going from methanol to dimethyl-sulphoxide. Also the Brönsted plot in dimethylsulphoxide was more steep than the plot obtained in methanol, that is, the intrinsic barrier in dimethylsulphoxide is lower than it is in methanol.

These results were explained by assuming that the solvent re-organisation energy altered when methanol was replaced by dimethylsulphoxide. It was assumed that ionisation of a CH-acid in a hydroxyl-containing solvent is accompanied by noticeable solvent re-organisation making this the main contribution to the total re-organisation energy. The solvent re-organisation was assumed to be concerted with proton transfer.

The Marcus theory has received theoretical support in more recently published work[549,567-569]. Dogonadze and Kuznetsov derived a formula for the energy of activation[567-568].

$$q^{\neq} + (E_r + Q)^2/4E_r \qquad (11)$$

where E_r is the solvent re-organisation energy.

This formula was derived for model reactions assuming that the proton is transferred, and only the dielectric continuum of the medium is changed, without any changes occurring in the structure of reactants and solvent in the inner co-ordination shell.

Using this model the E_r values calculated for the ionisation of beta--dicarbonyl compounds from the halogenation rates[570-572,568] were as follows.

	E_r, kcal/mole	E_r, kcal/mole
$CH_3COCH(CH_3)COOEt$	55.5	0.0 (standard)
$CH_3COCH(Br)COCH_3$	55.0	+ 0.5
CH_3COCH_2COOEt	50.9	- 4.6
$CH_3COCH_2COC_6H_5$	48.6	- 6.9
$CH_3COCH_2COCH_3$	50.9	-4.6
$(CH_2)_4COCHCOOEt$	50.9	-4.6

These data suggest that substitution at the carbon atom bearing the departing proton results in a higher solvent re-organisation energy (E_r) i.e., in a more essential charge redistribution. When the substituents are introduced to an atom lying farther from the reaction site the change in E_r is lower, therefore, compounds of the latter type should represent a unit structural series.

When proton transfer is accompanied by a change in the molecular structure of the reactants, the energy of activation contains both the term present in equation 11 ($q^{\neq}$) and the term responsible for structure re-organisation[568].

Kresge and Koeppl[569] assumed that a change in the structure of the reagent may affect the distance between the minima of the HA···B and A···HB energy terms. If so, $d\alpha/dQ$ will no longer be a constant at $q_b^{\neq}$ = constant and the dependence between α and the transition state structure will become more complicated.

III. "NORMAL" BRÖNSTED PLOTS

Brönsted plots should be non-linear over wide ΔpKa intervals. This is due in the case of fast reactions, to the diffusion limitations leading to $\alpha = 0$ ($\beta = 1$) or $\beta = 0$ ($\alpha = 1$). With slow reactions, non-linearity of Brönsted plots results from the intersection of energy curves.

Also, the non-linearity which has been experimentally observed may be an artifact due, e.g., to a contribution of the internal return mechanism (see Chapter III). Non-linearity of the Brönsted plots hinders conversion of the kinetic proton transfer data into the equilibrium CH-acidity parameters.

Nevertheless, linear Brönsted plots are often observed in narrower ΔpKa intervals for structurally similar acids. This is mainly due to the fact that the non-linearity is hardly observable in a narrow ΔpKa interval since it is lower than are the errors involved in measuring rates.

Brönsted correlations for some CH-acids are illustrated in Table 69. Correlations with "anomalous" slopes ($\alpha>1$ or $\alpha<0$) are excluded as these will be discussed in the following Section. The monograph by Bell[87] contains extensive tables of kinetic data on acid-base catalysis in organic reactions presented in terms of the Brönsted relation.

The Brönsted α value varies from ca. 0.4 (ΔpKa of 5 to 10 pKa units) to ca. 1 (ΔpKa of 15 to 20 pKa units), for methanol-containing solutions of CH-acids whose anions are strongly conjugated, such as fluorene, triphenylmethane, etc. These α patterns may be due to (i) a contribution by the internal return mechanism (Chapter III) which requires that the hydrogen exchange rate be related with ΔpKa by the relationship $\Delta \lg k_{obs} \simeq$ ΔpKa (i.e., that α be unity)

or (ii) a high structure re-organisation energy for proton transfer to the delocalised carbanion. When α is observed to be equal to unity, this may be due to internal return mechanism rather than non-barrier proton transfer (see Chapter III).

TABLE 69

Kinetic vs Thermodynamical CH-Acidity

CH-Acids	Solvent (catalyst)	α	Ref. No.
1. β-Keto esters, β-diketones, ketones, nitriles, etc.; pKa 5 to 20		0.6	34
	$H_2O(H_2O)$	0.5 to 1.0[a]	574
2. Carbonyl compounds	H_2O (O- or N-bases)	0.4 to 0.9[a]	87, 630
3. Cyclopentadiene, acetophenone, phenylacetylene, fluorene	D_2O-dimethylformamide (triethylamine)	0.4	151
4. Substituted fluorenes	$CH_3OD(CH_3ONa)$	0.4	64
5. Ph_2CH_2, Ph_3CH, fluorene, indene, etc.	$ND_3(ND_3)$	0.6	308
6. Ph_2CH_2, Ph_3CH, fluorene 9-phenylxanthene, etc; pKa 20 to 30	CH_3OD-$(CD_3)_2SO$ (CH_3ONa) 3/1	0.5 to 1[a]	348
7. Ph_3CH, substituted fluorenes etc.	a) dimethylsulphoxide /bases	0.4 to 1[a]	286
	b) $CH_3OD(CH_3ONa)$	0.4 to 1[a]	286
8. Monoaryl methanes (HMO calcns)	CHA(LiCHA)	ca. 1	573
9. $ArCH_2SO_2CH_3$	$CH_3OH(CH_3ONa)$	0.8	377
10. Carboranes	$ND_3(KND_2)$	0.6	76
11. Aliphatic nitro compounds	$H_2O(H_2O)$	0.8	575
Base-Catalysed Reactions.			
12. Bromination of carbonyl--compounds	$H_2O(RCOO^-)$	0.4 to 0.9 (β value[a])	434
13. Ionisation of nitroethane	H_2O(oxygen-containing anions, amines)	0.5 (β value[a])	576
14. Ionisation of nitro alkanes (calcd)	$H_2O(RCOO^-)$	0.5 to 0.7 (β value[a])	568

[a] Brönsted plots are not linear
LiCHA = lithium cyclohexylamide.

If the formation of carbanions is accompanied by bond rehybridisation leading

to charge delocalisation in the molecule, in other words, if the charge is distributed over the atoms neighbouring the C-H bond undergoing ionisation, then the reaction, inevitably leading to alteration of the geometry, will have a high structure and solvent re-organisation energy. The Brönsted slope versus rehybridisation pattern may be visualised by collating, for example, the proton transfer from sulphones with that from fluorene. Sulphones such as $ArCH_2SO_2CH_3$ ionised by sodium methoxide in methanol lead to an α value of 0.8 whereas for a series of substituted fluorenes whose acidity is comparable with that of sulphones α is 0.4, (Table 69). This may be explained by assuming that α observed is due not only to ΔpKa but also to rehybridisation in the transition state.

It is evident that in the region $0<\alpha<1$, the effect of conjugation on CH-acid ionisation rate at $\Delta pKa = 0$ is the opposite to the effect upon the acid strength. Conjugation stabilises a carbanion and thus lowers the ΔpKa value. This accelerates ionisation but, on the other hand, the ionisation constant will be lower than it would have been if the decrease in ΔpKa had not been accompanied by rehybridisation and charge delocalisation. The lower ionisation constants observed for conjugated CH-acids are due to a contribution by the re-organisation energies in the energy of activation. That is why α is relatively low in fluorenes: the slower the reaction the more prolonged the Brönsted plot, (see equation 8).

Examination of ionisation rates in various CH-acids acted upon by various bases may help to find how strongly rehybridisation affects the Brönsted coefficient. If the hardness (softness) remains invariable in the acid or base series chosen, then changing the base strength (for a given acid) or varying the acid strength (for a given base) should lead to two identical Brönsted plots, since this is equivalent to shifting the parabolas in Fig. 17, to the left or to the right along the vertical axis. This statement is more accurate if the energy terms are linear rather than parabolic. If the Brönsted slopes do differ it may be assumed than the re-organisation factor is not invariable in the series under study.

Different discrepancies between the slopes of the α- and β-plots have been observed for the transfer of proton occuring between 2,6-dinitro- or 2,4,6-trinitrobenzyl anions and various hydroxy-acids in ethanol[181,577,578]. The plots are presented in Fig. 18. The coefficient α is 0.44 for the trinitrobenzyl anion and 0.28 for the dinitrobenzyl anion, whereas β is 0.24 ± 0.03. The difference between α and β is higher in the case of the trinitrobenzyl anion because charge delocalisation is more favourable with this anion; flash-photolysis studies have shown that α varies from zero to unity for these two anions studied at a wide interval of (17) pKa units of hydroxy-acid strength[181].

Brönsted plots agree closely with the Hammett plots. The high Hammett ρ value observed for protophilic reactions infers that the transition state is highly carbanionic. Similarly, the Brönsted α value found for a simple proton transfer reaction is a characteristic of the charge distribution in the transition state[579,580].

The σ vs. ρ correlations for CH-acids have been discussed in Chapter III. Some of these correlations are quoted in Table 70.

IV. CORRELATIONS OF PROTON TRANSFER RATE WITH ACIDITY FUNCTION H-

The function H- is a measure of basicity in strongly basic media. Media of this kind may be made by, e.g., adding up to 40% of alkali or alkali alkoxide to a protic solvent. The most frequently used mixture nowadays is a mixture of dimethylsulphoxide and water and/or alcohols. H- measured in such solvents varies from 12 to about 29 depending on the concentration of water present. (Chapter I).

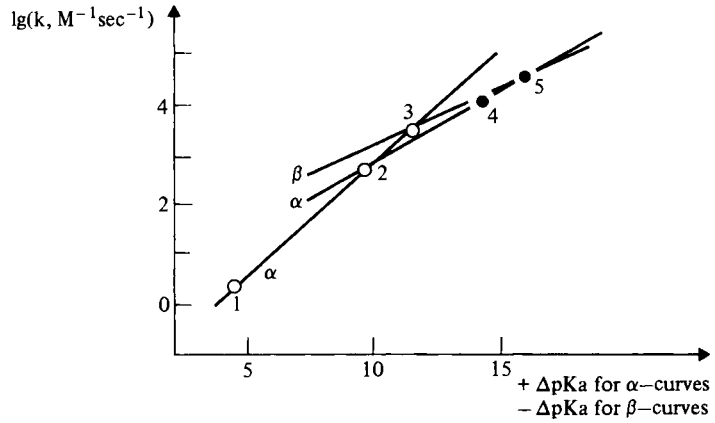


Fig. 18. Brönsted plots for proton transfer between 2,4,6-trinitrobenzyl anion or 2,6-dinitrobenzyl anion and OH-acids in methanol. OH-acids: PhOH (1), CH_3COOH (2 and 4), $CH_2ClCOOH$ (3 and 5). Open circles, $2,4,6\text{-}(NO_2)_3C_6H_2CH_2^-$; filled circles, $2,6\text{-}(NO_2)_2C_6H_3CH_2^-$.

TABLE 70

Examples of σρ-correlations

	Acids	Solvent (catalyst)	ρ	Ref. No.
1.	Substituted benzenes, hydrogen exchange in the ortho- or meta-positions	$ND_3(KND_2)$	12.6	323
2.	2-Substituted fluorenes-9-t	$CH_3OH(CH_3ONa)$	3.2	573
3.	Substituted toluenes- -t	CHA(LiCHA)	4.0	573

This Table does not include the numerous acidity vs. structure correlations that have been reviewed for nitro alkanes[631]. The complicated acidity vs. structure patterns have led to a great number of "correlations" including induction, steric hindrance, hyperconjugation, solvation, environment effects, and purely formal quantities such as the number of α- and β-hydrogen atoms present[632] as factors governing the pKa values. Such equations are not very informative and exemplify a purely formal approach to the problem of reactivity. In fact, any parameter included in a correlation should be tested by independent experiment, or substantiated by an independent theoretical approach[631].

The high increase in basicity observed in solvents which contain a high proportion of dimethylsulphoxide or another dipolar aprotic solvent, is due to the fact that such solvents solvate anions poorly[581]. Consequently, the γ_{A^-} value in equation 12 should increase with the concentration of dimethylsulphoxide in the aqueous alkali solution.

$$H_- = -\lg\frac{a_{H^+}\gamma_{A^-}}{\gamma_{AH}} = -\lg\frac{K_w a_{H_2O}\gamma_{A^-}}{a_{OH^-}\gamma_{AH}} \qquad (12)$$

where γ_{A^-} and γ_{AH} are the activity coefficients of the anion and neutral forms of the indicator and $K_w = (a_{H^+} + a_{OH^-})/a_{H_2O}$ is water ionisation constant and a_{H_2O} is the activity of water. The indicators HA (usually, hydrocarbons or amines) have a higher solubility in dimethylsulphoxide than in water, therefore, the addition of dimethylsulphoxide should decrease γ_{AH}. The joint action of these two effects increases H_-.

Equation (12) leads to an expression for the rates of base-catalysed reaction in dimethylsulphoxide/water mixtures[582 583].

$$k_{obs} \alpha\ h_-\ C_{H_2O}$$

It is assumed that the relationship is valid for a simple reaction limited by the proton abstraction step

$$\frac{\gamma_{A^-}}{\gamma_{HA}} = \frac{\gamma^{\neq}}{\gamma_{RH}} \qquad (13)$$

where γ_{A^-}, γ_{HA}, $\gamma^{\neq}$ and γ_{RH} are the activity coefficients of the anionic and neutral indicator forms, of the transition state, and of the non-ionised acid, respectively. Then the observed reaction rate versus the H_- function will be as follows[574].

$$\lg k_{obs} = H_- + \lg a_{H_2O} + \text{const} \qquad (14)$$

When deriving equation (14) it is taken that equation (13) is equivalent to an assumption that the transition state for proton abstraction has a structure very similar to the carbanion structure ($\alpha \rightarrow 1$). A better assumption, however, is that the equilibrium behaviour of the CH-acid coincides with the behaviour of the indicator, in other words that,

$$\frac{\gamma_{A^-}}{\gamma_{HA}} = \frac{\gamma_{R^-}}{\gamma_{RH}}$$

In a first-order reaction whose limiting step is proton transfer, the constant is

$$k_{obs} = k \cdot a_{OH^-}\ \frac{\gamma_{RH}}{\gamma^{\neq}}$$

Substituting the following relationship[584]

$$\gamma^{\neq} = \gamma_{R^-}^{\beta}\ \gamma_{RH}^{(1-\beta)}\ \gamma_{OH^-}^{(1-\beta)}\ \gamma_{H_2O}^{\beta}$$

then equation (15) is obtained

$$\lg k_{obs} = \beta H_- + \beta \lg a_{H_2O} + \text{const} \qquad (15)$$

where a_{H_2O} is the concentration of water, and β is the Brönsted coefficient. Equation (15) is equivalent to the Brönsted equation.

Comparison of equations (14) and (15) show that lgk_{obs} and H_- are linearly interrelated.

TABLE 71

Rate-equilibrium Correlations for Proton Transfer in Strongly Basic Media

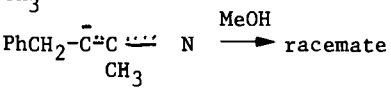
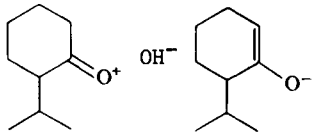
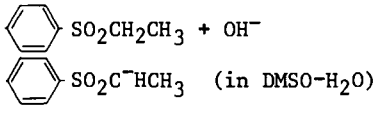
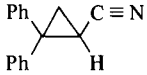
	Reaction	H-variation region, length	lgk vs H_-	Ref. No.
1.	$Ph-CH_2-\overset{H}{\underset{CH_3}{\overset{|}{C}}}-C\equiv N + MeO^-$(MeOH-DMSO) 	ca. 9	0.87	585
2.	$CHCl_3 + MeO^-$(MeOH $\longrightarrow CCl_3^-$ + MeOH	ca. 2	0.8	586
3.	$PhCOCH_2T + OH^- \longrightarrow PhCOCH_2^- + HOT$ $+ MeO^- \longrightarrow PhCOCH_2^- + MeOT$ $+ EtO^- \longrightarrow PhCOCH_2^- + EtOT$ (in DMSO-H_2O(MeOH, EtOH))	ca. 5	0.54-0.42 0.40 0.30	587
4.	$CH_3SOCH_3 + OH^-$(MeO^-, EtO^-) $\longrightarrow CH_3SOCH_2^-$ (in DMSO-H_2O(MeOH, EtOH))	ca. 8	0.93	588
5.	$Ph_3CH + MeO^- \longrightarrow Ph_3C^- + MeOH$ $Ph_2CH_2 + MeO^- \longrightarrow Ph_2CH^- + MeOH$	ca. 1.5	0.8	348
6.	Fluorene + MeO^-(MeOH) $\longrightarrow C_{13}H_9^-$	ca. 3	0.98	64
7.	$PhCH_2-CH_2-S^+(CH_3)_2 + OH^-$ $\longrightarrow PhCH_2-C^-H-S^+(CH_3)$ (in DMSO-H_2O)	ca. 4	ca. 0.7	442,589
8.	 (in DMSO-H_2O	ca. 6	0.48	443
9.	$PhCH_2CH_2Br + t\text{-}BuO^- \longrightarrow PhCH=CH_2 +$ $+ tBuOH + Br^-$ (in DMSO-t-BuOH)	ca. 1	above 2	441
10.	 (in DMSO-H_2O)	ca. 4	0.7	574
11.	 + MeO^- $\longrightarrow$ racemate (in DMSO-MeOH)	ca. 8	1.0	590

TABLE 71 - *continued*

Reaction	H-variation region, length	lgk vs H-	Ref No.
12.  $-CH_2CH = CH_2 + OH^- \longrightarrow$  $-CH = CHCH_3$ (in DMSO-H_2O)			
X = H	ca. 3	0.77	591
m-Cl	ca. 4	0.77	
p-Cl	ca. 3	0.79	
m-CH_3	ca. 3	0.79	
m-OCH_3	ca. 4	0.79	
13. $Ph_2CHC{\equiv}CPh + OH^- \longrightarrow Ph_2C = C = CHPh$ (in DMSO-H_2O)	ca. 2	0.84	591
14. $CTCL_3 + OH^- \longrightarrow CCl_3^- + HOT$ (in DMSO-H_2O)	ca. 3	0.98	373
15. $CNCH_2CH{=}CHCH_2CN + OH^- \longrightarrow CNCH_2CH{=}CHCH^-CN$ (in DMSO-H_2O)	ca. 3	0.71	373

DMSO = dimethylsulphoxide

Table 71 shows correlations of proton transfer rate constants with the proton -acceptor activity of the medium (see also reference 160, 282, 592 and 543).

If the lgk_{obs} versus H- slope has been measured for a substrate then, to visualise the structure of the transition state, it is necessary to assume that the concept of H- function is valid for the substrate under study and this is not always necessarily so.

Even if it is assumed, a priori, that function H- is indeed valid for a given case, a correlation will still be possible only under the following conditions[574], (i) that the reaction mechanism should be clear and the limiting step should be verified as being due only to proton abstraction occuring under the action of the base; (ii) that the reaction rate should be measured at a maximally wide H- interval and at a temperature as close as possible to the temperature at which the ionisation equilibrium has been studied; (iii) that the reaction is carried out under the conditions under which ion association is either absent from the solution or may be readily taken into account.

In practice, one or more of these conditions are usually violated. Consequently, any interpretation of the plots of lgk_{obs} versus H- (Table 71) should be approached with caution.

One possible interpretation is that the slope is a measure of C-H bond ionisation in the transition state. The slopes in Table 71 vary from 0.3 to 1, it exceeds unity only in the case of the reaction involving the elimination of hydrogen bromide from 2-Br-1-phenylethane catalysed by tert-butoxide (Reaction 9, Table 71). This deviation has been ascribed to ion-pair catalysis[574]. The ion-pair effect is a very strong one and its existance cannot be ignored in rate or equilibrium studies. This is especially so in the case of concentrated solutions of bases or in dipolar aprotic solvents containing low concentrations of water or alcohols. In systems of this kind, solvation of the base with water or alcohol is poor, so the energy is decreased due to association with the metal cation. Quantitative data on the association of alkoxide and hydroxyl alkali cations is discussed in Chapter I.

The effects of ion-pairs on the acidity function H_- has been extensively studied[64,348,594-598]. H_- values found in 5 M solutions of various alkali hydroxides are as follows[594],

potassium hydroxide	15.45
sodium hydroxide	14.87
lithium hydroxide	14.31

This corresponds to an increase in association across the series K<Na<Li (the ion-pair HO^-M^+ dissociation constants for the cations are: K 5.1, Na 3.4, Li 1.5[574]). The H_- values found in concentrated solution of the above alkali metal hydroxides should be corrected for the concentrations of ion-pairs present. This has been done by Jones[574] who showed that H_- is a linear function of the dissociated fraction of the base, not the total concentration.

The addition of neutral salts to the system acetophenone/base decreases the base-catalysed proton abstraction rate as follows: K<Na<Li<Ba<Ca<Mg[596,597]. The series corresponds to that describing the ability of the cations to associate with hydroxy ions.

TABLE 72

Brönsted β values for Proton Abstraction from some CH-Acids acted upon by Hydroxyl Anions[574].

Acid	pKa (see Ch. I)	β_{OH^-}	$d\lg k_{obs}/dH_-$
$CH_3COCHCl_2$	16	0.29	
CH_3COCH_2Cl	16.5	0.29	
$C_6H_5COCH_3$	19		0.47
CH_3COCH_3	20	0.54	
(-) Menthone	21		0.48
$p\text{-}ClC_6H_4SO_2CH_2CH_3$	23-25		0.70
$Ph_2CHC{\equiv}CPh$	ca. 30		0.84
CH_3SOCH_3	33		0.93
$CHCl_3$	15; 24[373]		0.98

The concentration of the ion-pair $HO^-(RO^-)M^+$ in solution may be found by

measuring the difference between the second-order CH-acid deprotonation rate constants determined at a high and a low base concentration. If ion-pair catalysis does not occur then the ion-pair concentration found from the deprotonation rates will coincide with that found by an alternate method and, indeed this is commonly found to be the case[599-603].

Jones[574] has discussed the applicability of the acidity function H_- concept to CH-acids. He collated the β_{OH^-} values obtained by Bell[604] with $\lg k_{obs}$ vs. H_- slopes (shown in Table 71) for a number of CH-acids covering a pKa interval of 17 units. The results are summarised in Table 72. The β_{OH^-} values, which characterise the slope of a plot of $\lg k_{obs}$ versus $pK_a(B^-)$ at the point corresponding to $B^- = OH^-$, and the slope of a plot of $\lg k_{obs}$ versus H_- are in parallel with each other. They are closer to unity for the weaker CH-acids, chloroform being an exception. This agrees with the results based on the energy curve approach.

V. BRÖNSTED PLOTS WITH ANOMALOUS SLOPES

It follows from the preceding Section that, theoretically, the Brönsted coefficient cannot be less than zero or greater than unity for a series of reactions, whether the reactions be fast or slow. The inequality $0<\alpha<1$ is usually interpreted as meaning that the effect of substituents upon the free energy change ($q^{\neq}$) in proceeding from the ground state to the transition state has the same sign as has the difference (Q) between the free energies of the initial state and the final state, with $q^{\neq}$ never exceeding Q. In other words, the assumption is that the movement of the system along the reaction co-ordinate is continued and smooth throughout and the structure of the transition state resembles that of both the initial and the final structures[579,605].

However, reactions are known whose experimental α values are either negative or exceed unity. They were first discovered experimentally and a more or less reliable interpretation of these observations has now been formulated, as discussed below.

Anomalous Brönsted plots are exemplified in Table 73. Except for two cases (Systems 3 and 7), all the anomalous Brönsted coefficients observed have been obtained in cases of proton transfer from nitroalkanes and, in fact, the term "nitroalkane anomaly" has been proposed for this effect[609]. Nitroalkanes are pseudo-acids whose behaviour may be represented as follows.

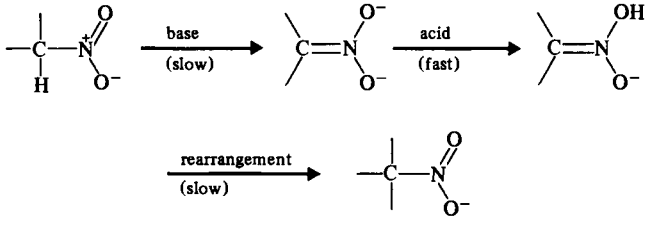


TABLE 73

Anomalous Brönsted Plots

	Acid Series	Base	Solvent	α	Ref No.
	I. Systems with α<0 unity				
1.	R_2CHNO_2 (R = H or CH_3)	OH^-	H_2O	-0.48	22, 43 34
2.	$(CH_2)_n$ $CHNO_2$ (n = 2,3)	OH^-	H_2O	-0.3	377
3.	$RCOCH_2COR$ (R = CH_3 or CF_3)	H_2O	H_2O	-0.2	274
	II. Systems with α>0 unity				
4.	$ArCH_2NO_2$	OH^-	H_2O	1.54	607
		morpholine	H_2O	1.29	607
		2,6-lutidine	H_2O	1.30	607
5.	$ArCH(CH_3)NO_2$	OH^-	H_2O	1.14	607
		OH^-	50%H_2O-dioxan	1.17	731
		OR^-	50%H_2O-MeOH	1.37	236 377
6.	$ArCH_2CH(CH_3)NO_2$	OR^-	50%H2O-MeOH	1.61	236
7.	ArOH (with intramolecular H-bond)	OH^-	H_2O	1.21	608
8.	$RCHClNO_2$ (R = A-1. Ar)	OAc^-	H_2O	1.23	606

Nitrocompounds ionise to produce nitronate ions the negative charge of which is mainly localised on the oxygen of the nitro group. Consequently, these anions can only formally be considered as carbanions. Proton abstraction from a nitroalkane should, therefore, proceed via a transition state of the structure intermediate between that of the nitroalkane and the acid-anion. Accordingly, the process may be expected to have a rather high structure and solvent re-organisation energy. The Marcus theory suggests that anomalous Brönsted coefficients are more likely to occur with pseudo-acids than with "normal" acids such as OH- or NH-[557].

In 1969, Marcus[557] proposed a theory of anomalous Brönsted plots. He introduced an expression for α, which is more complicated than occurs in the case of equation (8). This equation assumes that the intrinsic reaction barrier ($q_0^{\neq}$) is invariable over the reaction series being considered. By eliminating this assumption Marcus arrived at equation (16).

$$\alpha = \frac{dq^{\neq}}{dQ} = \frac{1}{2}\left(1+\frac{Q}{4q_0^{\neq}}\right) + 1\left[-\frac{Q}{4q_0^{\neq}}^2\right]\frac{dq_0^{\neq}}{dQ} \qquad (16)$$

When the internal barrier is invariable (i.e. $dq_o^{\neq}/dQ = 0$) then equation (16) transforms to equation (8). The Marcus theory is valid at $-4q_o^{\neq}<Q<4q_o^{\neq}$, so when $dq_o^{\neq}/dQ = 0$ then α lies between zero and unity (equation 8). If, however, $dq_o^{\neq}/dQ \neq 0$, then α may be lower than zero or higher than unity.

Considering the reaction of a nitroalkane with hydroxide ion.

$$R_1R_2CHNO_2 + OH^- \longrightarrow R_1R_2CNO_2^- + H_2O$$

According to Marcus, the internal barrier may be expressed by the equation,

$$q_o^{\neq} = \frac{q_{NA}^{\neq} + q_{OH}^{\neq}}{2}$$

where $q_{NA}^{\neq}$ and $q_{OH}^{\neq}$ are, respectively, the energies of activation of the following reactions

$$R_1R_2CHNO_2 + R_1R_2CNO_2^- \xrightarrow{\Delta pKa = 0} R_1R_2CNO_2^- + R_1R_2CHNO_2$$

and

$$H_2O + OH^- \xrightarrow{\Delta pKa = 0} OH^- + H_2O.$$

The second reaction is very fast hence $q_{OH}^{\neq}$ is low and $q_o^{\neq} \simeq (1/2)q_{NA}^{\neq}$. For the nitroalkanes quoted in Table 73 α is less than zero, so equation (16) ($q_o^{\neq} \simeq (1/2)q_{NA}^{\neq}$) is applicable. This leads to the important conclusion that the change in nitroalkane structures is, alone, responsible for the change in internal barriers.

Dogonadze and Kuznetsov applied their theory (equation 11) to the calculation of re-organisation energies in reactions of nitroalkanes with hydroxide ion in water. The ΔE_r values (kcal/mole) calculated from the experimental activation energies and pKa's were as follows[568]. It is evident that all the three compounds have essentially different energies.

CH_3NO_2	0.0	(standard)
$CH_3CH_2NO_2$	9.5	
$(CH_3)_2CHNO_2$	-4.0	

Considering the reactions of a nitroalkane with a series of acids.

$$\gtrless CHNO_2 + B \longrightarrow \gtrless CNO_2^- + HB^+$$

The internal barrier is in this case given by the relation,

$$q_o^{\neq} = \frac{q_{NA}^{\neq} + q_B^{\neq}}{2}$$

where $q_B^{\neq}$ is the activation energy of the reaction

$$B + HB^+ \longrightarrow HB^+ + B$$

In this series, $q^{\neq}_{NA}$ is a constant and, if the bases B are oxygen or nitrogen, $q^{\neq}_{B}$ will also be nearly constant. Hence, $q^{\neq}_{O}$ is a constant, that is, normal Brönsted plots ($0<\beta<1$) should be observed for reactions of a nitroalkane with a series of bases. Indeed, β has been found to be 0.5 for the ionisation of nitroethane under the action of nitrogen-containing bases[610] and β is 0.4 (or 0.55)[436] for the ionisation of 2-nitropropane[375].

It should be noted that the $dq^{\neq}_{O}/dQ$ behaviour which leads to anomalous α values may be due both to anomalous changes in $q^{\neq}_{O}$ (the changes that do not agree with polar substituent effects upon rates of reactions of the type) and anomalous Q changes. In this connection, it is profitable to compare the ionisation of nitroalkanes with the ionisation of substituted acetylacetones (Systems 1 and 3, Table 73).

TABLE 74

Substituent Effect upon Kinetic and Equilibrium Acidities of Nitroalkanes and Acetyl Acetones[22,34,43,373].

CH-Acid series	pKa	k_{rel}	Comment
CH_3NO_2	10.2	113	
$CH_3CH_2NO_2$	8.5	18	pKa is abnormal
$(CH_3)_2CHNO_2$	7.7	(1.0)	
$CH_3COCH_2COCH_3$	8.99	4.4	
$CF_3COCH_2COCH_3$	6.79	2.2	k_{rel} is abnormal
$CF_3COCH_2COCF_3$	5.3	(1.0)	
$CF_3COCH_2COC_6H_4OCH_3$-p	6.94	0.3	
$CF_3COCH_2COC_6H_5$	6.54	0.52	no anomalies
$CF_3COCH_2COC_6H_4NO_2$-p	5.38	(1.0)	

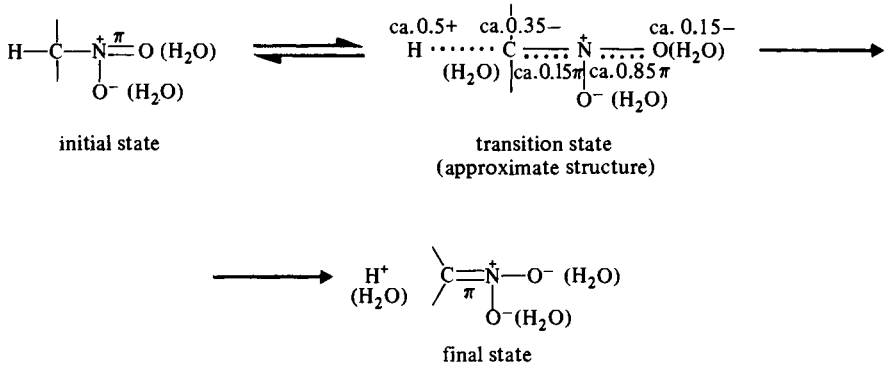
The data of Table 74 show that in the nitroalkane series it is the pKa pattern that does not fit in with conventional substituent effects whereas in acetylacetones the proton abstraction rate behaves anomalously.

In the nitroalkanes, methyl groups substituted successively for the alpha--hydrogen atom decelerate the proton abstraction which agrees with the known positive induction effect of methyl groups. On the other hand, owing to hyperconjugation (Chapter II), equilibrium acidity increases across the series nitromethane, nitroethane, 2-nitropropane. These facts suggest that the transition state for the ionisation of nitroalkanes differs significantly from the final product, nitronate ion. Bordwell et al[236] who studied transition states of deprotonation of nitroalkanes with hydroxide ion in water believed that the C-H bond fission and hydroxy bond formation occur to an approximately equal extent, whereas the resulting negative charge is rather insignificantly delocalised on the oxygen of the nitro group. In other words, the transition state is carbanionic.

The result obtained by Bordwell et al[236] agree with the data obtained by Davies[611] Kresge et al[612] and Bordwell et al[236] on secondary isotope exchange

during the deprotonation of 2-nitropropane. The conclusion of these workers was that methyl hyperconjugation only operates weakly in the transition state, and very strongly in the nitronate anion. The extent of proton transfer is close to 0.5 for the ionisation of 2-nitropropane in aqueous alkaline solutions, but the C-N double bond order is about 15-20%[612]; therefore, hyperconjugation cannot play any significant role in this process.

A question arises as to whether the transition states for the ionisation of nitroalkanes in alkaline media are product-like or reactant-like. So far, there is no ambigous answer to this question. The transition state is reactant-like from the point of view of the criterion of the order of the C-N double bond, it lies near to midway between that of the products and the reactants as estimated from charge separation data. In the case of nitroethane, Davies[611] has shown that the charge separation data suggests that the transition state is as follows.



This scheme shows that, unlike its geometry, the polarity of this nitroalkane is considerable affected on going from the initial to the transition state. Consequently, the main contributor to the total re-organisation energy is solvent (water) re-organisation rather than structure re-organisation. Ritchie and Ushold[286] believe that solvent is "in process of re-organisation" at the instant of the formation of the transition state and its configuration is not an equilibrium one, that is, does not correspond to the charge distribution in the transition complex. Moelwyn-Hughes and Glew[613] consider solvent re-organisation as a process directly preceding the rupture and formation of chemical bonds. Regardless of the mechanism, solvent re-organisation may play a leading role in deciding the total energy of activation of the reaction.

Solvent re-organisation is caused by the occurrence of a charge redistribution in moving from the ground state to the transition state, but solvent re-organisation energy is, generally speaking, not a function of charge distribution in the transition complex, so it cannot be expected that the change in the reaction rate in changing from one solvent to another will be governed exclusively by the change in the reaction equilibrium constant via the Brönsted equation.

In Chapter II it was shown how spectroscopy has demonstrated that the charge distribution in nitronate ions depends on the nature of the solvent. The negative charge on the carbon atom is more pronounced in dipolar aprotic solvents than it is with protic solvents, that is, the anions of nitro-compounds more closely resemble carbanions in aprotic solvents than they do in protic solvents, such as water. Consequently, the anomalous effect exhibited by alphamethyl groups upon the equilibrium acidity of nitroalkanes should be less in the case of dipolar aprotic solvents than it is in water. This observation is in agreement with the following data obtained by Faleev et al[614] and Belikov et al[615].

	ΔpKa	
	in water	in dimethylsulphoxide
CH_3NO_2 (standard)	(0.0)	(0.0)
$CH_3CH_2NO_2$	1.6	0.3
$(CH_3)_2CHNO_2$	2.5	0.7

Consequently, the slope of the Brönsted plot obtained in dimethylsulphoxide may be expected to be, if not positive, at least less negative than it is in water. This conclusion still waits verification since the ionisation rates of nitroalkanes in dimethylsulphoxide have not yet been measured.

Acetylacetone, trifluoroacetylacetone, and hexafluoroacetylacetone form a series (Table 74) which differ from the nitroalkanes, it is the kinetic not the equilibrium acidity which is anomalous. The successive introduction of three and then six fluorines increases the equilibrium acidity, which is in agreement with the expected stabilisation of the carbanion by the fluorine negative inductive effect. At the same time the kinetic acidity decreases. This anomalous change in kinetic acidity can hardly be explained by polar effects of the fluorine substituents. The only alternative possibility is that solvation by water plays a role. It might be possible to resolve this question by measuring the rates of substituted acetylacetones in aprotic solvents such as dimethylsulphoxide. However, measurements of this kind have not yet been made.

Belikov et al[378] and Faleev[204] in their work on kinetic versus thermodynamic parameters, studied the mechanism of the condensation of 1,1-dinitroethane or methyl alpha-nitropionate anions with acetyldehyde in water and in dimethylsulphoxide. They found that the limiting step in the acid-catalysed addition of the nitro anions to carbonyl group was as follows.

$$CH_3 - CH\begin{matrix}X\\NO_2\end{matrix} \quad \underset{\text{fast}}{\overset{Ka}{\rightleftharpoons}} \quad CH_3 - C\begin{matrix}X\\(-\\NO_2\end{matrix} \quad + H^+ \text{ solv}$$

$$CH_3 - C(X)(NO_2) + CH_3CHO + HA \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3-C(X)(NO_2)-CH(OH)-CH_3 + A^- \qquad (17)$$

$$A^- + H^+ \text{ solv} \underset{\text{fast}}{\overset{K_\beta}{\rightleftharpoons}} AH$$

(X = NO_2 ot COOMe)

The total equilibrium constant (K_{eq}) may be expressed in terms of the equilibrium constants of the carbon-carbon bond formation proper, (K_{CC}), as follows:

$$K_{eq} = K_a K_b K_{CC} = K_a K_b \frac{k_1}{k_{-1}}$$

This equation gives K_{CC} as a function of the experimental values of K_{eq}, K_a, and K_b. The constant K_{CC} characterises the affinity of the nitro anions for the carbonyl carbon in protonated acetaldehyde. The K_{CC} and k_1 values are listed in Table 75 which demonstrates that in aqueous solutions there exists an anomalous relationship between the equilibrium affinity and the kinetic affinity of nitro anions for the carbonyl carbon of acetaldehyde. In water, when the anion $(CH_3C(NO_2)COOCH_3)^-$ is replaced by the anion $(CH_3C(NO_2)_2)^-$ the constant K_{eq} decreases in value because of the increase in the mesomeric effect between the acetate group and the nitro group.

TABLE 75

Equilibrium and Kinetical Affinities of 1,1-dinitroethane and Methyl α-nitropropionate anions for the Carbonyl Carbon of Acetaldehyde, in Water or in Dimethylsulphoxide[204].

Anion	In water		In Dimethylsulphoxide	
	$K_{CC} = \frac{K_{eq}(M^{-2})}{K_a}$	k_1[a] $(M^{-1}sec^{-1})$	$K_{CC} = \frac{K_{eq}(M^{-2})}{K_a}$	k_1[b] (M^2sec^{-1})
$CH_3C(NO_2)_2^-$	5.21×10^6	0.463	1.2×10^9	1.5
$CH_3C(NO_2)COOCH_3^-$	38.4×10^6	0.196	5400×10^9	75

[a] HA = H_2O)eq. 17); [b] HA = Et_3NH^+ (eq. 17)

However, the constant k_1 increases to a striking degree. If this anomaly is indeed caused by solvation effects, it may be expected that in dimethylsulphoxide the situation will be different, since in this solvent the anions are not subject to specific hydrogen-bond solvation which governs the relative chemical potentials of anions in a given solvent. Indeed. there are no anomalies in dimethylsulphoxide (Table 75). In water, the anion is eight times less active thermodynamically, than is the methyl alpha-nitropropionate anion, its kinetic activity is twice as high (i.e. β = -0.3), whereas in dimethylsulphoxide both the equilibrium and the kinetic acidities of the dinitroethane anion are lower by a factor of 4500 and 50, respectively (β = 0.47) than they are for the methyl alphanitropropionate

anion. Thus, the replacement of water by dimethylsulphoxide would bring about the expected relationship between basicity and nucleophilicity, a stronger base becomes a stronger nucleophile. It is concluded that the anomalies observed in aqueous solutions are caused by the specific solvation of anions by hydrogen bonds.

These results can be interpreted in terms of the solvent shell re-organisation that occurs in the reaction complex before the formation or decomposition of covalent bonds begins to operate. In Fig. 19 is shown an energy profile assumed for the reaction of the dinitroethane and the methylalphanitropropionate carbanions in water, one of these being assumed to be more basic and more highly solvated.

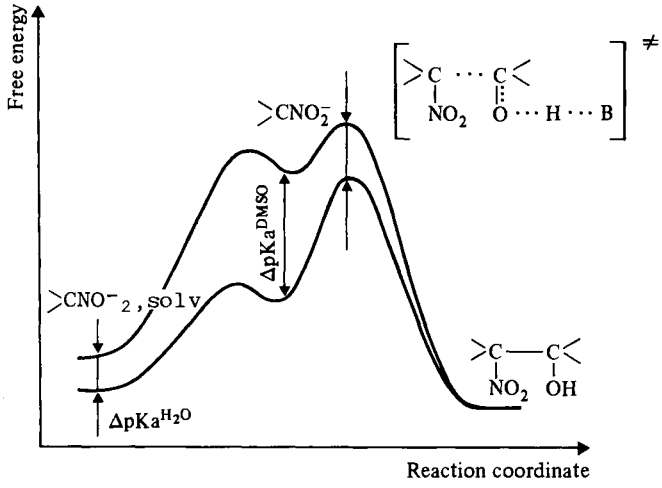


Fig. 19. Free energy profile of nucleophilic addition for two nitronate ions in water (Plot from Ref. 378).

The difference between the free energies of the solvated carbanions is close to the ΔpK_a value of the respective acids in water, ($\Delta pK_a^{H_2O}$). Assuming that before they enter into the reaction with carbonyl group the carbanions are desolvated and, if the solvent shell is completely removed, the free energy difference for the "naked" anions will be close to the ΔpKa value of the conjugate acids in dimethylsulphoxide, (ΔpK_a^{DMSO}). (In Chapter I it was suggested that acidity in dimethylsulphoxide is a better measure of intrinsic acidity than is the acidity in water). A typical protic solvent, water, may reduce the acidity by preferentially solvating anions of weaker acids, in cases when these anions are relatively strong bases whose negative charge is less delocalised. Therefore, $\Delta lg(K_{eq}/K_a)^{H_2O}$ may be lower than $\Delta lg(K_{eq}/K_a)^{DMSO}$. Since C-C bonds are partially formed in the transition state, the difference between the free energies of the transition states may be equal to $\beta\Delta lg(K_{eq}/K_a)^{DMSO}$, where β is the Brönsted coefficient. It is also possible that $\Delta lk(K_{eq}/K_a)^{H_2O} < \beta\Delta lg(K_{eq}/K_a)^{DMSO} < \Delta lg(K_{eq}/K_a)^{DMSO}$, in

which case the free energy of activation observed for the more basic participant is higher than that observed for the other one. That is why the nucleophilicity/basicity anomaly plays a part when the solvent is water and is non-existent in dimethylsulphoxide, an observation that is in accord with experiment.

Belikov et al[204,378] have proved that the above reaction does not involve anions solvated by hydrogen bonds. They determined the logarithmic rate constants for the decomposition of a series of nitro alcohols and showed that $\lg k_{-1}$ in water (eq. 17) varies with the pKa measured in dimethylsulphoxide, but not with that measured in water.

Consequently, the anomalous Brönsted slopes found for the C-C bond formations discussed above are due to solvation effects.

The protonation rates for the dinitroethane and the methylalphanitropropionate anions do not lead to anomalous Brönsted plots, but the calculated β value (ca. 0.1) is so low as to suggest the reaction is anomolous.

The following data

	pKa	$k_1 (M^{-1}sec^{-1})$ for reaction with H_3O^+	
$CH(NO_2)_2^-$	5.18	3.1×10^3	$\beta \simeq 0.1$
$CH(NO_2)COOCH_3^-$	6.40	4.2×10^3	

show that these two anions differ in their acidity by 1.2 pKa units and in their protonation rate by 1.1×10^3 units. Accordingly, in dimethylsulphoxide the β values will be closer to 0.5 (after correcting for the acid/base ΔpKa). This suggests that the anomalous acidity pattern observed in fluorosubstituted acetylacetones may become normal if dimethylsulphoxide were used as solvent.

The Brönsted slope is normal ($\alpha = 0.3$) for ring-substituted trifluorobenzoylacetones (Table 74). This may be due to the fact that the negative charge is strongly delocalised in these "soft" anions, so the hydrogen-bond solvation is less pronounced.

In conclusion, therefore, it can be stated that the bulk of the experimental evidence shows that anomalous Brönsted plots are caused by the effect of hydroxyl-containing solvents. Consequently, data obtained when water is used as solvent should be used with caution in correlations of equilibrium and kinetic acidity.

The second part, II, of Table 73 describes the reactions for which α is greater than unity. Formally, the equation $\alpha > 1$ means that the effect of a substituent upon the free energy of activation is higher than it is upon the heat of reaction[232,236], in other words, kinetic acidity is more substituent-sensitive than is equilibrium acidity. Since $\alpha + \beta = 1$, then β is less than zero, and the substituents which accelerate (slow down) the removal of protons from a CH-acid also accelerate (slow down) the protonation rate of carbanions. This subtituent effect pattern is typical of CH-acids in aqueous solution, but not of hydroxy-acids. The only known exception is the $\alpha > 1$ anomaly in phenol whose ionisation is hindered by the intramolecular hydrogen bond (System 7, Table 73). The explanation of this may be that

substituent effect in CH-acids is a sum of various effects such as induction, conjugation and steric hindrance. The relative contributions made by these effects may differ during the stabilisation of the carbanion and, on the other hand, of the carbanionic transition state. Thus, conjugation works to its fullest extent in nitroalkane anions whereas it is almost completely absent in the ionisation transition state of these pseudo-acids (see above). On the other hand, the ionisation of hydroxy-acids causes a build-up of negative charge on the oxygen atom and this charge does not delocalise over the other atoms since oxygen is a strongly electronegative element. Consequently, substituents in hydroxy (or NH-) acids have an effect on the forward and on the inverse reactions in the opposite direction, thus leading to the normal Brönsted plots.

It is worthwhile noting that all anomalous Brönsted plots have been obtained in aqueous solutions containing oxygen-bases. Probably, the anomalous values observed are all due to solvation effects. Consequently, it would be profitable to study the ionisation rates of CH-acids in aprotic solvents and in the gas phase.

VI. H_2O/OH^- SYSTEM

The investigation of acid-base catalysis in terms of the Brönsted principle has long since made it evident that hydroxonium and hydroxide ions usually deviate from the straight line relationship on which the other, non-solvent-derived catalytical species lie. Table 76 shows some reactions of CH-acids catalysed by hydroxide ion. Proton abstraction is in all cases the slowest step.

The accurate estimation of hydroxide ion basicity in aqueous solutions is a difficult problem. A conventional assumption is that the free water K_a in water amounts to 1.8×10^{-16}, obtained as follows.

In the reaction

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^- \qquad (18)$$

The equilibrium constant is $K_{H_2O} = (H_3O^+)(OH^-)/H_2O)(H_2O)$. Since $(H_3O^+)(OH^-)/(H_2O)$ is 10^{-14} and the free water concentration in water is 55 mole/l, the resulting water acidity is $K_{H_2O} = 10^{-14}/55 = 1.8 \times 10^{-16}$ corresponding to a pKa of 15.7. Bell[604] noted that the difficulties are due to the fact that liquid water is a hydrogen-bonded polymer containing a relatively low amount of free monomeric water molecules. In other words, water is a diluted solution of water monomer in a polymeric solvent. Only water monomer is involved in equation (18), and its concentration is less than 55 m/l, consequently the real $pKa(H_2O)$ is lower than 15.7, the OH^- ion deviation will become less pronounced when it is negative but more pronounced when it is positive.

The anomalous behaviour of hydroxonium and hydroxide ions has been explained in terms of the non-linearity of Brönsted plots[166], electrostatic effects[627] and hydrogen bonding effect upon the forward and inverse proton transfer reactions[373]. These theories are, however, not fully satisfactory since they explain only the negative, not the positive deviations.

The best explanation of this anomalous behaviour is based on the well-known fact that hydroxonium (H_3O^+) and hydroxide ions can very easily merge in the liquid water structure, so they are more strongly solvated than are other

acids and bases[362]. Desolvation of the ions requires the consumption of extra energy, thus the reaction barrier increases as do the negative deviations from the Brönsted plot. It is noteworthy, however, that the decelerating effect works only if the substrate itself does not form strong hydrogen bonds with the solvent, otherwide the Grotthuss chain proton transfer mechanism may interfere. The latter mechanism does not need the inclusion of desolvation. Moreover, unlike other acids and bases, hydroxonium and hydroxide ions are favoured by the chain mechanism and lead, therefore, to positive departures from the Brönsted plot.

TABLE 76

Hydrogen Substitution in CH- and OH-acids Catalysed by OH^- Ions[554].

	Reaction	k_{obs}, $M^{-1}sec^{-1}$	$\lg \frac{k_{obs}}{k_{calcd}}$	Ref.No.
	CH-Acids			
1.	Iodination of CH_3COCH_3	$2.5x10^{-1}$	-3.54	617,618
2.	Iodination of $CH_3COCH_2CH_2COCH_3$	1.7	-3.74	617,618
3.	Iodination of CH_3COCH_2Cl	9.3	-3.43	617,618
4.	Iodination of CH_3COCH_2Br	$2.0x10^2$	-2.92	617,618
5.	Bromination of $CH_3COCHCl_2$	$4.5x10^2$	-2.71	617,618
6.	Detritiation of PhC≡CT	$2.5x10^2$	-2.10	362
7.	Ionisation of NO_2CH_2COOEt	$1.5x10^5$	-2.57	619
8.	Detritiation of NO_2-C_6H_4 -CT_2CN	26	-1.65	620
9.	Detritiation of $CNCH_2CH{=}CHCF_2CN$	$2.1x10^{-1}$	-3.0	621
	OH-Acids			
10.	Decomposition of nitramide (NH-acid)	2×10^4	-3.0	618,622
11.	Glucose mutaroation	$6.4x10^2$	-0.71	624,618.623
12.	Hydration of CH_3CHO	8×10^4	+1.31	625
13.	Dehydration of $CH_2(OH)_2$	$1.6x10^3$	+0.90	626

This theory agrees with the fact that all reactions which lead to the negative departures (except for nitramide decomposition) are reactions of CH-acids (Table 76). CH-acids are only poorly solvated by water, the chain mechanism does not operate, hence the negative deviation. On the other hand, all reactions which display the positive deviation are proton transfer reactions of hydroxy-acids (Table 76). The reaction site in the substrate is hydrogen-bonded with water, so proton transfer may proceed via the chain mechanism hence the positive deviation from the Brönsted plot.

VII. CONCLUSION

The data discussed in this Chapter has shown that, although a correlation (a non-linear one at wider ΔpKa intervals) might, on theoretical grounds, be expected between equilibrium and kinetic acidities, this is rather difficult to observe experimentally[628]. The main interfering factors are (i) a possible contribution of the internal return mechanism, (ii) the ion-pair effects, and (ii) hydrogen bonding effects involving the formation

and decomposition of hydrogen bonds with the solvent in the course of the reaction.

These effects often lead to significant scattering in lgk vs. ΔpKa plots. In some cases, anomalous slopes ($\alpha<0$ or $\alpha>1$) are observed. The anomalous Brönsted plots have been observed only in protic media: probably, the anomalies are mainly due to solvent effects. Consequently, it is only with extreme caution that a C-H bond ionisation rate can be taken as a measure of the relative strength of the CH-acid or relative stability of the carbanion.

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